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FILE 'HOME' ENTERED AT 22:31:56 ON 27 SEP 2007

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                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'REGISTRY' ENTERED AT 22:32:09 ON 27 SEP 2007
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STRUCTURE FILE UPDATES:   26 SEP 2007  HIGHEST RN 948239-70-1
DICTIONARY FILE UPDATES:  26 SEP 2007  HIGHEST RN 948239-70-1

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TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

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REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=> s benzodiazepine and dimethoxy and ethyl and methyl and dimethoxyphenyl
         46059 BENZODIAZEPINE
        849177 DIMETHOXY
       8641602 ETHYL
            13 ETHYLS
       8641602 ETHYL
                 (ETHYL OR ETHYLS)
      19398317 METHYL
            97 METHYLS
      19398317 METHYL
                 (METHYL OR METHYLS)
        392011 DIMETHOXYPHENYL
L1         135 BENZODIAZEPINE AND DIMETHOXY AND ETHYL AND METHYL AND DIMETHOXYP
               HENYL

=> s l1 and 5H
        530627 5H
L2          71 L1 AND 5H

=> s l2 and 4-methyl
      20158339 4
      19398317 METHYL
            97 METHYLS
      19398317 METHYL
                 (METHYL OR METHYLS)
       2022956 4-METHYL
                 (4(W)METHYL)
L3          57 L2 AND 4-METHYL

=> s l3 and 2-ethyl
      24020984 2
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    8641602 ETHYL
         13 ETHYLS
    8641602 ETHYL
              (ETHYL OR ETHYLS)
     333214 2-ETHYL
              (2(W)ETHYL)
L4         0 L3 AND 2-ETHYL

=> d l3 1-57

L3   ANSWER 1 OF 57  REGISTRY  COPYRIGHT 2007 ACS on STN
RN   914303-51-8  REGISTRY
ED   Entered STN:  29 Nov 2006
CN   5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-
     4-methyl-, (1R,5S)- (9CI)  (CA INDEX NAME)
MF   C22 H26 N2 O4
SR   CA
LC   STN Files:   CA, CAPLUS
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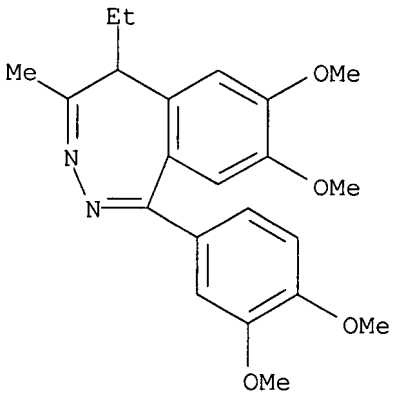


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              1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3   ANSWER 2 OF 57  REGISTRY  COPYRIGHT 2007 ACS on STN
RN   914303-50-7  REGISTRY
ED   Entered STN:  29 Nov 2006
CN   5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-
     4-methyl-, (1S,5S)- (9CI)  (CA INDEX NAME)
MF   C22 H26 N2 O4
SR   CA
LC   STN Files:   CA, CAPLUS
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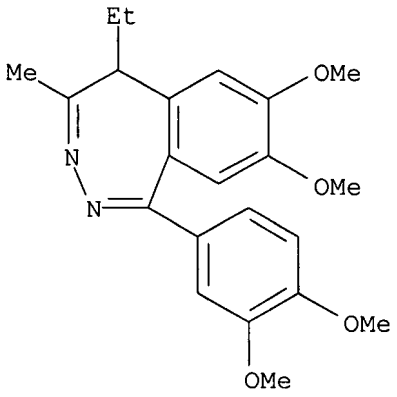
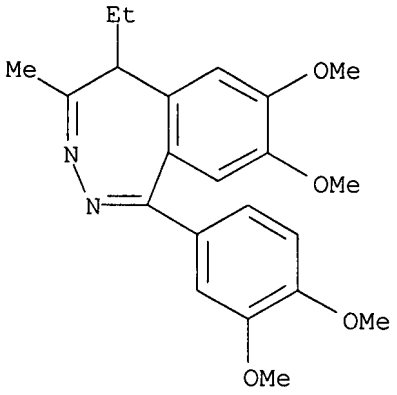


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 3 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 914303-49-4 REGISTRY
ED Entered STN: 29 Nov 2006
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (1R,5R)- (9CI)** (CA INDEX NAME)
MF C22 H26 N2 O4
SR CA
LC STN Files: CA, CAPLUS



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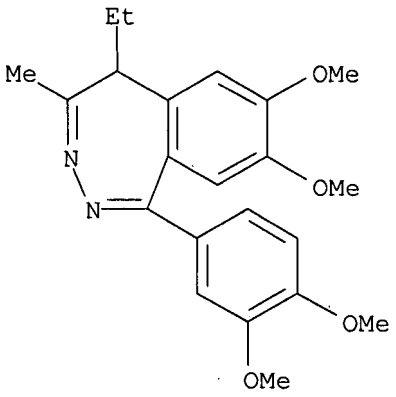
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 4 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 914303-48-3 REGISTRY
ED Entered STN: 29 Nov 2006
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (1S,5R)- (9CI)** (CA INDEX NAME)
MF C22 H26 N2 O4
SR CA
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 5 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 869940-28-3 REGISTRY
ED Entered STN: 15 Dec 2005
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-7,8-diethoxy-5-ethyl-4-methyl-** (CA INDEX NAME)
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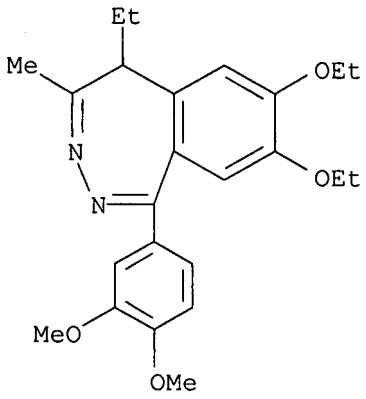
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

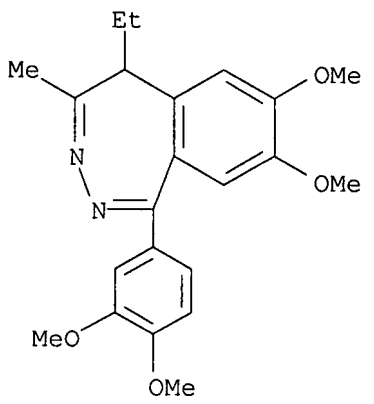


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 6 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 869940-21-6 REGISTRY
ED Entered STN: 15 Dec 2005
CN **5H-2,3-Benzodiazepine-7,8-diol, 1-(3,4-dimethoxyphenyl)-5-ethyl-4-methyl-, (5S)-** (CA INDEX NAME)
FS STEREOSEARCH
MF C20 H22 N2 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

L3 ANSWER 57 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 22345-47-7 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-** (CA INDEX NAME)
OTHER NAMES:
CN **1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine**
CN **7,8-Dimethoxy-1-(3,4-dimethoxyphenyl)-5-ethyl-4-methyl-5H-2,3-benzodiazepine**
CN EGYT 341
CN Grandaxin
CN Seriel
CN Tofisopam
DR 87555-18-8
MF C22 H26 N2 O4
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, PS, RTECS*, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL, USPATOLD
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



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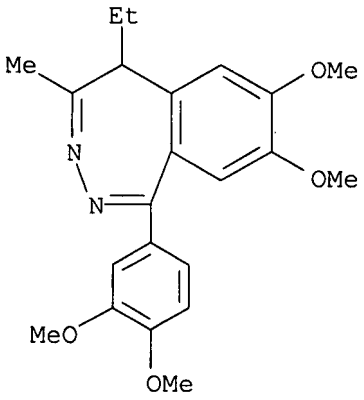
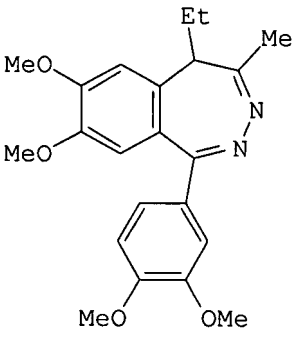
211 REFERENCES IN FILE CAPLUS (1907 TO DATE)



L7 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1981:473687 CAPLUS
DOCUMENT NUMBER: 95:73687
TITLE: Pharmacological studies of **tofisopam**. 2
AUTHOR(S): Ito, Chihiro; Shibutani, Yasunori; Suzuki, Kazuo; Yamaguchi, Kazuo; Noguchi, Katsuhiko; Yamazaki, Yoshio; Ohnishi, Haruo
CORPORATE SOURCE: Res. Lab. Pharmacol., Mochida Pharm. Co. Ltd., Tokyo, Japan
SOURCE: Iyakuhin Kenkyu (1981), 12(2), 587-600
CODEN: IYKEDH; ISSN: 0287-0894
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
GI

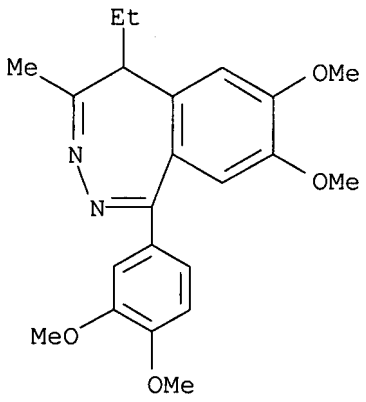


I

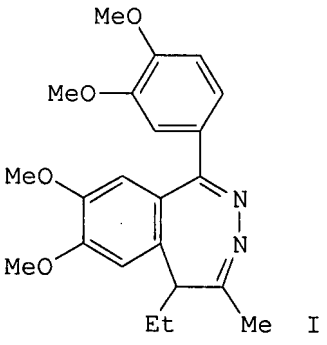
AB The pharmacol. effects of **tofisopam** (I) [**22345-47-7**] were studied in vivo and in vitro. Spontaneous locomotion and acetic acid-induced stretching were inhibited, **body temp.** was decreased, and pain threshold was elevated by oral I; these effects were similar to but lower in potency than those of diazepam. I.v. I was hypotensive in rabbits. I induced vasodilation in vitro. The drug inhibited adrenaline-induced arrhythmia and vasopressin-induced angina pectoris. At high concns., I relaxed isolated smooth muscule organs. I had no surface or infiltrative anesthetic activity, and had no effect on the neuromuscular junction, erythrocyte membrane, paw edema formation, vascular permeability, blood sugar level, or coagulation system.

IT **22345-47-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. of)

RN 22345-47-7 CAPLUS
CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



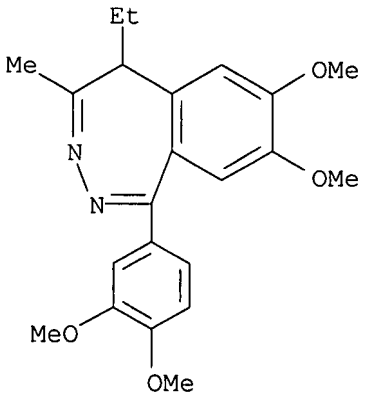
L7 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1984:412141 CAPLUS
DOCUMENT NUMBER: 101:12141
TITLE: Production of microcapsules containing **tofisopam**
AUTHOR(S): Devay, Attila; Racz, Istvan
CORPORATE SOURCE: Semmelweis Orvostud. Egy. Gyogyszereszeti Intez., Budapest, 1092, Hung.
SOURCE: Acta Pharmaceutica Hungarica (1984), 54(2), 84-9
CODEN: APHGAO; ISSN: 0001-6659
DOCUMENT TYPE: Journal
LANGUAGE: Hungarian
GI



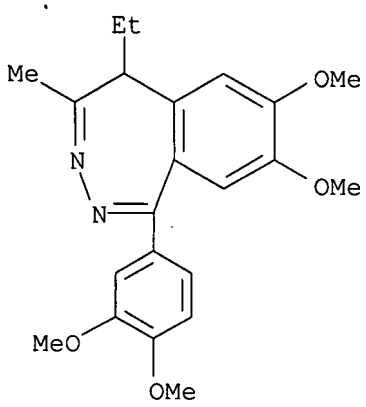
I

AB **Tofisopam** (I) [**22345-47-7**] was microencapsulated by melt dispersion, using cetyl alc. and Et cellulose as matrix materials. The particle size (x0) and homogeneity factor (n) of the capsules depended on the preparation **temp.**, mixing rate, mixing time, and ratio between the internal and external phase of the disperse system. The x0 decreased with **temp.**, in the 65-90° range, and with an increase in mixing rate. The n was maximum at 80°.
IT **22345-47-7**
RL: PROC (Process)
(microencapsulation of)
RN 22345-47-7 CAPLUS
CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-

methyl- (CA INDEX NAME)



L7 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:709076 CAPLUS
DOCUMENT NUMBER: 121:309076
TITLE: A new method of studying **temperature** dependence and the effect of mobile phase composition on the retention mechanism in reversed phase liquid chromatography
AUTHOR(S): Guillaume, Y.; Guinchard, C.
CORPORATE SOURCE: Laboratoire de Chimie Analytique, UFR des Sciences Medicales et Pharmaceutiques, Besancon, 25030, Fr.
SOURCE: Journal of Liquid Chromatography (1994), 17(13), 2809-20
CODEN: JLCHD8; ISSN: 0148-3919
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A rapid procedure is used to examinate the effect of **temp.** and eluent composition on thermodn. properties in high performance liquid chromatog.
is presented. The use of an exptl. design is proposed to study thermodn. solution property trends for 10 benzodiazepines. Enthalpies and entropies of transfer (mobile to stationary phase) are calculated by evaluation of Van't Hoff plots. Enthalpies of transfer are neg for all cases examined. These data show that the entropy contribution to retention becomes more significant as solvent polarity decreases. The enthalpy-entropy compensation behavior is tested for varying mobile phase composition
IT **22345-47-7, Tofisopam**
RL: ANT (Analyte); ANST (Analytical study)
(eluent composition and **temp.** effects on retention mechanism in reversed phase liquid chromatog. and enthalpy-entropy compensation)
RN 22345-47-7 CAPLUS
CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



L7 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:472492 CAPLUS
DOCUMENT NUMBER: 139:53044
TITLE: Process for the preparation of **tofisopam** and new intermediates
INVENTOR(S): Molnarne Samu, Erika; Simig, Gyula; Vago, Pal; Greff, Zoltan
PATENT ASSIGNEE(S): Egis Gyogyszergyar Rt., Hung.
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003050092	A2	20030619	WO 2002-HU141	20021212
WO 2003050092	A3	20031106		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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HU 200105326	A2	20030929	HU 2001-5326	20011213
HU 200105326	A3	20051128		
HU 225411	B1	20061128		
HU 200105327	A2	20030929	HU 2001-5327	20011213
HU 200105327	A3	20051128		
AU 2002348942	A1	20030623	AU 2002-348942	20021212
EP 1465879	A2	20041013	EP 2002-781451	20021212
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BG 108801	A	20050430	BG 2004-108801	20040713

PRIORITY APPLN. INFO.:
HU 2001-5326 A 20011213
HU 2001-5327 A 20011213
WO 2002-HU141 W 20021212

OTHER SOURCE(S): CASREACT 139:53044; MARPAT 139:53044
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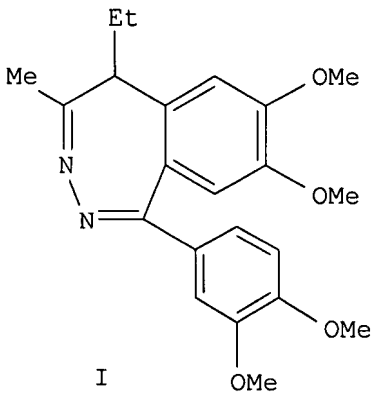

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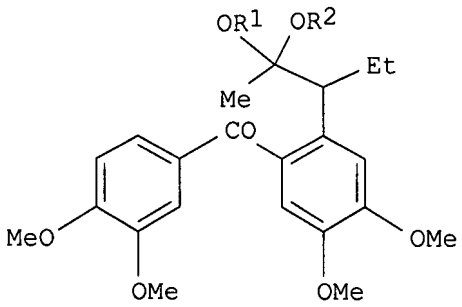


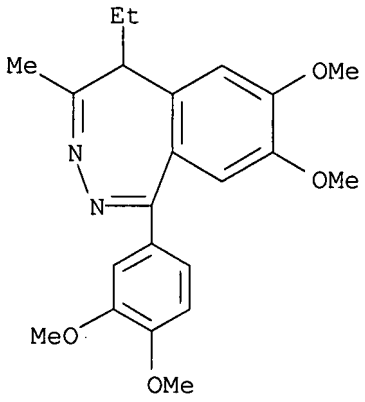
II

AB The invention relates to a new process for the preparation of 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine (I) that comprises reacting II (R1 and R2 independently each stands for C1-4-alkyl or together form C2-6-alkylene) with hydrazine or a hydrate or salt thereof formed with an inorg. or organic acid. I is a known anxiolytic agent. The invention also relates to new intermediates and a process for the preparation thereof. For example, I was prepared (84%) from II (R1OCOR2 = COCH2CH2O): to a mixture of 150 mmol of 99% HOAc and 90 mmol of 37% aqueous HCl, 30 mmol of II and 20 mL of MeOH were added; the mixture was stirred under boiling for 20 min, whereupon 120 mmol of 98% hydrazine monohydrate was added in several portions; the reaction mixture was subjected to post-reaction at this **temp**. for 30 min, made alkaline, cooled and the precipitated product was filtered and dried. II (R1OCOR2 = COCH2CH2O) was prepared (65%) from 0.05 mol 3-(2-bromo-4,5-dimethoxyphenyl)pentan-2-one ethylene ketal (III) in 173 mL of THF cooled to -78° to which was added 0.06 mol BuLi as a 2.5 M hexane solution followed by 0.125 mol 3,4-dimethoxybenzaldehyde. III was prepared (92%) from 0.11 mol 3-(2-bromo-4,5-dimethoxyphenyl)pentan-2-one (IV) in 250 mL of toluene to which was added 0.20 mol ethylene glycol and 1.5 g of p-toluenesulfonic acid. IV was prepared (85%) from 0.50 mol 3-(3,4-dimethoxyphenyl)pentan-2-one in 500 mL of EtOH to which was added 0.52 mol N-bromosuccinimide. The drawback of known procedures resides in the fact that the precursor 1-phenyl-2-benzopyrilium salts and the benzoylphenylacetone derivative can be prepared only with low yields in numerous reaction steps. A further disadvantage of the known procedures is that during the synthesis Cr salts being extremely detrimental to the environment are formed.

IT **22345-47-7P**, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine
RL: SPN (Synthetic preparation); PREP (Preparation)
(process for preparation of **tofisopam** and new intermediates)

RN 22345-47-7 CAPLUS

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



L7 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:1080692 CAPLUS
DOCUMENT NUMBER: 142:56375
TITLE: Modulation of dopamine responses with substituted (S)-2,3-benzodiazepines
INVENTOR(S): Leventer, Steven M.; Harris, Herbert W.; Kucharik, Robert F.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 33 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004254173	A1	20041216	US 2003-461290	20030613
PRIORITY APPLN. INFO.:			US 2003-461290	20030613

OTHER SOURCE(S): MARPAT 142:56375
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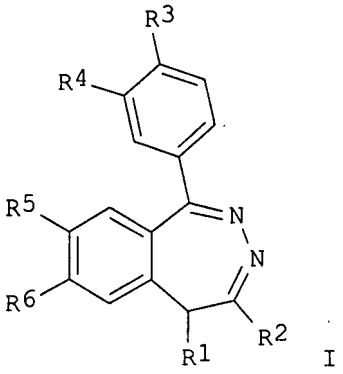


I

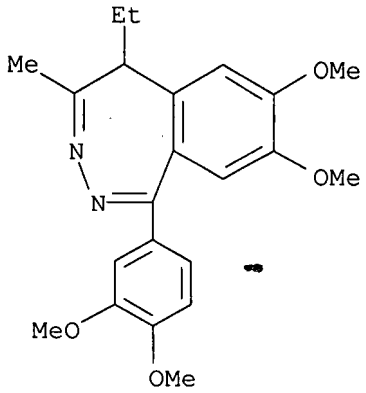
AB There is provided a method of modulating dopamine responses in the central nervous system of an individual or a method of treating a dopamine-mediated disorder in an individual not suffering from seizures or convulsions which comprises administering to the individual an effective amount of at least one compound of formula (I) [R1 = C1-7 hydrocarbyl or C2-6 heteroalkyl; R2 = H, C1-7 hydrocarbyl; wherein R1 and R2 may combine to form a carbocyclic or heterocyclic 5- or 6-membered ring; R3, R4, R5, R6 = OH, C1-7 hydrocarbyl, CF3, C1-7 hydrocarbyloxy, acyloxy, NH2,

-NH(C1-6alkyl), -N(C1-6 alkyl)2, -NH-acyl, halogen; wherein R5 and R6 may combine to form a 5-, 6- or 7-membered heterocyclic ring] or pharmaceutically acceptable salts thereof or said compound comprising an (S)-enantiomer substantially free of the (R)-enantiomer of the same compound The above dopamine-mediated disorder comprises a neurol. disorder or a neuropsychiatric disorder. The neurol. disorder includes Huntington's chorea, Parkinson's disease, periodic limb movement syndrome, restless leg syndrome, hyperkinesias, Tourette's syndrome, Pick's disease, punch drunk syndrome, progressive subnuclear palsy, multiple systems atrophy, Landau-Kleffner syndrome, benign essential blepharospasm, amyotrophic lateral sclerosis, medication-induced movement disorders, and cognitive disorders. The neuropsychiatric disorder includes psychosis, personality disorders, psychiatric mood disorders, conduct and impulse disorders, schizophrenia, bipolar disorders, dysphoric mania, anxiety disorders, depression, panic disorders, agoraphobia, obsessive-compulsive disorders and eating disorders. Thus, 4.41 g (10 mmol) 1-(3,4-dimethoxyphenyl)-3-methyl-4-ethyl-6,7-dimethoxyisobenzopyrilium chloride hydrochloride was dissolved in methanol (35 mL) at a **temp**. of 40°. After cooling to 20-25°, hydrazine hydrate (0.75 g, 15 mmol, dissolved in 5 mL methanol) was added and the resulting mixture was allowed to react while monitoring the reaction by HPLC and when complete, was evaporated to dryness. The residue was triturated with cold water (3 mL), filtered and dried to yield the crude 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine (racemic **tofisopam**) which was subsequently triturated with hot EtOAc to yield the pure product. Racemic **tofisopam** was resolved by a Chirobiotic V column (ASTEAC, Whippany, N.J.) to give (R)-**tofisopam** and (S)-**tofisopam**. (R)-**tofisopam** did not affect apomorphine-induced hypothermia in mice. Racemic **tofisopam** at 64 mg/kg tended to behave as a weak dopamine antagonist, i.e., lowering the rectal **temp**. at the thirty and sixty minute time points. However this trend was not statistically significant. (S)-**tofisopam** behaved as a weak dopamine antagonist at the 16 mg/kg dose at sixty minutes after apomorphine administration, i.e., showing a slight but statistically significant elevation in **temp**. At the higher doses, (S)-**tofisopam** demonstrated dopamine antagonism at both the thirty minute and sixty minute time points, i.e., lowering the rectal **temp**. at both time points.

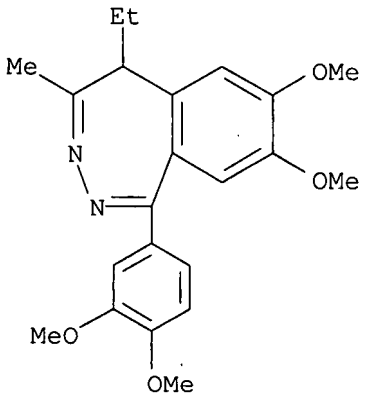
IT **22345-47-7P**, 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of (S)-2,3-benzodiazepines for modulation of dopamine responses and treatment of neurol. disorders or neuropsychiatric disorders)

RN 22345-47-7 CAPLUS

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



L7 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:68450 CAPLUS
DOCUMENT NUMBER: 120:68450
TITLE: Optimizing mobile phase composition, its flow rate and column **temperature** in HPLC using an experimental design assisted with a simplex method
AUTHOR(S): Guillaume, Y.; Guinchard, C.
CORPORATE SOURCE: Lab. Chim. Anal., UFR Sci. Med. Pharm., Besancon, Fr.
SOURCE: Journal of Liquid Chromatography (1993), 16(16), 3457-70
CODEN: JLCHD8; ISSN: 0148-3919
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A rapid procedure to sep. 10 benzodiazepines in HPLC is presented. The use of a modified G. E. P. Box and D. W. Behnken (1951, 1960, 1978) exptl. design assisted by a simplex method is proposed to sep. these compds. with only 13 chromatog. analyses to select the mobile phase composition, its flow rate and the column **temp**.. A flow rate of 0.77 mL/min with a percentage of MeOH of 49.95% in the mixture MeOH-H2O and a column **temp**. of 51.62° gave the most efficient separation conditions.
IT **22345-47-7, Tofisopam**
RL: ANST (Analytical study); PROC (Process)
(separation of, from benzodiazepines by HPLC and chemometrics involving simplex optimization)
RN 22345-47-7 CAPLUS
CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



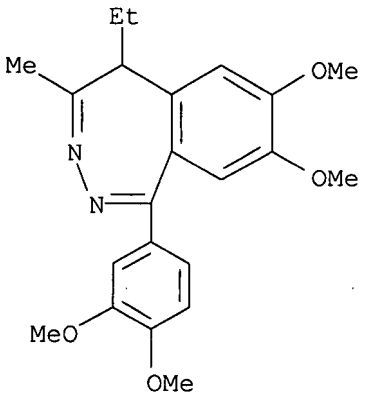
L7 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1995:449789 CAPLUS
DOCUMENT NUMBER: 123:198216
TITLE: Thermodynamic behavior of mixed benzodiazepines by a new liquid chromatographic method
AUTHOR(S): Guillaume, Y.; Guinchard, C.
CORPORATE SOURCE: Lab. Chim. Analytique, Fac. Sci. Med. Pharm., Besancon, 25030, Fr.
SOURCE: Chromatographia (1995), 40(3/4), 193-6
CODEN: CHRGB7; ISSN: 0009-5893
PUBLISHER: Vieweg
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Using a rapid chemometric methodol. to determine the separation factor, α, at different **temps**., Gibbs helmholtz parameters (Δ(ΔH), Δ(ΔS), Δ(ΔG)) of two adjacent benzodiazepines on a chromatogram were obtained from ln α vs. T-1 plots. A **temp**

. dependent reversal of the elution order was studied and the mobile phase composition and column **temp**. were optimized to obtain the best separation A flow rate of 0.80 mL. min-1 with 52.6% methanol in the methanol-water mixture and a column **temp**. of 48°C gave the most efficient separation of ten benzodiazepines.

IT **22345-47-7, Tofisopam**
RL: ANT (Analyte); PRP (Properties); ANST (Analytical study)
(thermodn. of mixed benzodiazepines by liquid chromatog.)

RN 22345-47-7 CAPLUS

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



L7 ANSWER 13 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1999:425036 CAPLUS

DOCUMENT NUMBER: 131:204699

TITLE: Influence of ionic strength and organic modifier on performance in capillary electrochromatography on phenyl silica stationary phase

AUTHOR(S): Cahours, X.; Morin, Ph.; Dreux, M.

CORPORATE SOURCE: B.P. 6759, UPRES-A 6005, CNRS, Institut de Chimie Organique et Analytique, Orleans, 45 067, Fr.

SOURCE: Journal of Chromatography, A (1999), 845(1 + 2), 203-216
CODEN: JCRAEY; ISSN: 0021-9673

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

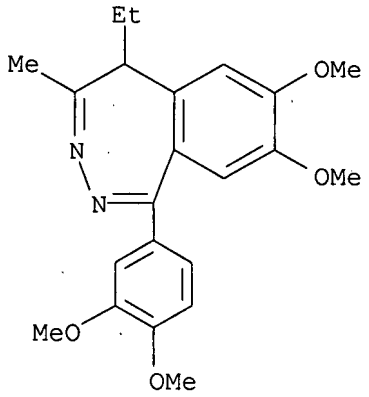
AB The effect of 3 physicochem. parameters (**temp**., ionic strength and organic modifier content of the hydroorg. buffer) upon electrophoretic (electroosmotic flow, EOF, chromatog. retention factor and separation (retention time and peak efficiency)) performances was carefully investigated in capillary electrochromatog. (CEC) on a Ph bonded silica column. Five benzodiazepines (diazepam, lorazepam, oxazepam, temazepam, and **tofisopam**) were selected as test solutes. From the CEC results, an increase of the organic modifier content induces an increase of EOF and peak efficiency and a decrease of retention factor. Concerning the ionic strength parameter, an increase of the ionic strength undergoes a decrease of EOF and retention factor and an increase of peak efficiency. Finally, higher **temp**. of the column involves an increase of EOF and peak efficiency and a decrease of retention factor. So, the modification of ionic strength and **temp**. in CEC can mainly be interpreted as a CE-like behavior at the opposite of organic modifier content which acts as a LC-like behavior.At last, the CEC separation of these benzodiazepines was achieved in 18 min, using Tris (pH 8)-MeCN (60:40) mixture, ionic strength 5 mM as mobile phase, and a 3 μm phenyl-bonded silica as stationary phase. High peak efficiencies (200 000 theor.

plates/m) and resolns. of 1.5 were easily obtained.

IT **22345-47-7, Tofisopam**
RL: ANT (Analyte); ANST (Analytical study)
(ionic strength and modifier effect on capillary electrochromatog. of drugs on Ph silica stationary phase)

RN 22345-47-7 CAPLUS

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1995:805194 CAPLUS

DOCUMENT NUMBER: 123:358104

TITLE: Marked differences between acetonitrile/water and methanol/water mobile phase systems on the thermodynamic behavior of benzodiazepines in reversed phase liquid chromatography

AUTHOR(S): Guillaume, Y.; Guinchard, C.

CORPORATE SOURCE: Lab. Chimie Analytique, Fac. Sciences Medicales Pharmaceutiques, Besancon, 25030, Fr.

SOURCE: Chromatographia (1995), 41(1/2), 84-7
CODEN: CHRGB7; ISSN: 0009-5893

PUBLISHER: Vieweg

DOCUMENT TYPE: Journal

LANGUAGE: English

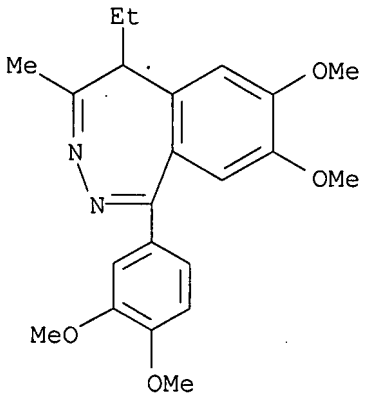
AB Two different methods were used to determine the separation factor α at different **temps**. and the Gibbs-Helmholtz parameters (Δ(ΔH),Δ(ΔS)) of two adjacent benzodiazepines on a chromatogram were obtained from plots of ln α vs. 1/T. The authors 1st studied each factor (fraction of water ϕ in the ACN/water mixture and column **temp**. T), which controls the retention mechanism, and then the authors examined the simultaneous variation of all these factors. The changes in Δ(ΔH) and Δ(ΔS) in relation to a volume fraction of water ϕ in an ACN/water mixture were examined In the ACN/water system, Δ(ΔH) was fairly constant in the acetonitrile region of $\phi \leq 0.52$ and appears to be a roughly linear function of ϕ for $\phi \geq 0.52$. In this system Δ(ΔS) is approx. a parabolic function of ϕ with an optimum at $\phi \approx 0.52$. The retention mechanism of ten benzodiazepines is significantly different in the methanol/water and ACN/water mixts. The separation optimization of these ten benzodiazepines was then considered. A fraction of water of 0.43 in the ACN/water mixture and a column **temp**. of 44°C gave the most efficient separation conditions in the ACN/water mixture

IT **22345-47-7, Tofisopam**

RL: ANT (Analyte); PRP (Properties); ANST (Analytical study)
(marked differences between acetonitrile/water and methanol/water mobile phase systems on thermodn. behavior of benzodiazepines in reversed phase LC)

RN 22345-47-7 CAPLUS

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



L7 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:669275 CAPLUS

DOCUMENT NUMBER: 136:47693

TITLE: Chiral supercritical fluid chromatography on porous graphitic carbon using commercial dimethyl β-cyclodextrins as mobile phase additive

AUTHOR(S): Salvador, A.; Herbreteau, B.; Dreux, M.; Karlsson, A.; Gyllenhaal, O.

CORPORATE SOURCE: Universite d'Orleans, UPRES A CNRS 6005, Institut de Chimie Organique et Analytique, Orleans, F-45067, Fr.

SOURCE: Journal of Chromatography, A (2001), 929(1-2), 101-112
CODEN: JCRAEY; ISSN: 0021-9673

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

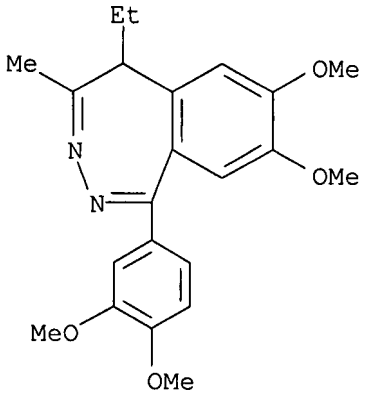
LANGUAGE: English

AB Using dimethylated-β-cyclodextrin mixts. (MeCD) as chiral selectors in CO2-polar modifier mobile phase and porous graphitic carbon as solid-phase, chiral supercrit. (or subcrit.) fluid chromatog. was performed. The adsorbed quantity of MeCD onto the porous graphitic carbon (Hypercarb) was measured for various chiral selector concns. using the breakthrough method with evaporative light scattering detector. The effects of MeCD concentration in the mobile phase, the nature of the polar modifier, the outlet pressure, the column **temp**. and the nature of the com. MeCD mixture on the retention and the enantioselectivities were studied. For a given solute, the enantioselectivity is greatly dependent on the com. MeCD mixture used. The retention mechanism was also studied. The dominant mechanism for the chiral discrimination is the diastereoisomeric complexation in the mobile phase.

IT **22345-47-7, Tofisopam**
RL: ANT (Analyte); PEP (Physical, engineering or chemical process); ANST (Analytical study); PROC (Process)
(analyte; chiral supercrit. fluid chromatog. on porous graphitic carbon using com. di-Me β-cyclodextrins as mobile phase additive)

RN 22345-47-7 CAPLUS

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



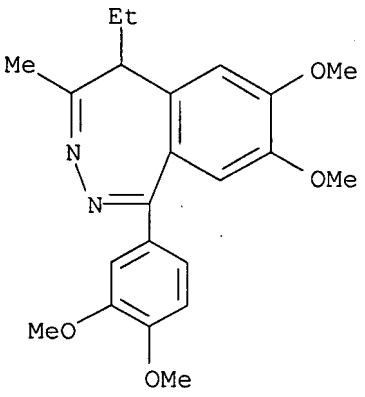
REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 16 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:314905 CAPLUS
DOCUMENT NUMBER: 120:314905
TITLE: Study and optimization of column efficiency in HPLC: comparison of two methods for separating ten benzodiazepines
AUTHOR(S): Guillaume, Y.; Guinchard, C.
CORPORATE SOURCE: Lab. Chim. Anal., UFR Sci. Med. Pharm., Besancon, Fr.
SOURCE: Journal of Liquid Chromatography (1994), 17(7), 1443-59
CODEN: JLCHD8; ISSN: 0148-3919
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To understand the influence of mobile phase composition, its flow rate and column **temp.** involved in high performance Liquid Chromatog., an exptl. design was used. The observed responses were the theor. plate number, the linear velocity of the mobile phase and a new chromatog. resolution function which provided the most efficient separation of 10 compds. as 10 benzodiazepines. Optimum conditions obtained were compared with another optimization method.

IT **22345-47-7, Tofisopam**
RL: ANST (Analytical study)
(separation of, from benzodiazepines by HPLC, optimization of column efficiency in)

RN 22345-47-7 CAPLUS
CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)

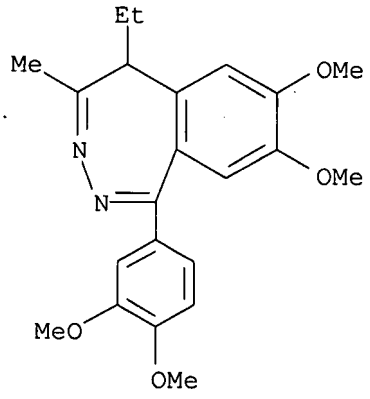


L7 ANSWER 17 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:347589 CAPLUS
DOCUMENT NUMBER: 126:321141
TITLE: A new approach to study benzodiazepine separation and the differences between a methanol/water and acetonitrile/water mixture on column efficiency in liquid chromatography
AUTHOR(S): Guillaume, Y.; Cavalli, E. J.; Peyrin, E.; Guinchard, C.
CORPORATE SOURCE: Laboratoire de Chimie Analytique, Faculte de Medecine Pharmacie, Besacon, 25030, Fr.
SOURCE: Journal of Liquid Chromatography & Related Technologies (1997), 20(11), 1741-1756
CODEN: JLCTFC; ISSN: 1082-6076
PUBLISHER: Dekker
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A chemometric methodol. was used to study column efficiency and the separation of 10 benzodiazepines in reversed phase liquid chromatog. New simple math. models and the organic modifier (OM) organization of ACN in the water, explained differences on column efficiency observed when ACN is chosen instead of CH3OH. A new response function, which takes into account the separation quality and the anal. time, was proposed for the separation optimization.

The result, a mobile phase ACN/water (60/40)(V/V), with a flow rate = 1.00 mL/min and a column **temp.** = 47°C were optimum values for a rapid chromatog. separation

IT **22345-47-7, Tofisopam**
RL: ANT (Analyte); ANST (Analytical study)
(separation of benzodiazepines by reversed-phase HPLC)
RN 22345-47-7 CAPLUS
CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

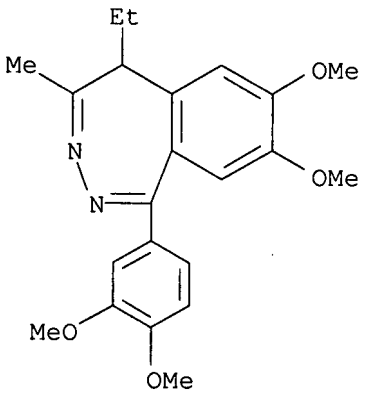
L7 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:455986 CAPLUS
DOCUMENT NUMBER: 125:157339
TITLE: Retention Mechanism of Weak Polar Solutes in Reversed Phase Liquid Chromatography
AUTHOR(S): Guillaume, Yves Claude; Guinchard, Christiane
CORPORATE SOURCE: Laboratoire de Chimie Analytique, Faculte de Medecine et Pharmacie, Besancon, 25030, Fr.
SOURCE: Analytical Chemistry (1996), 68(17), 2869-2873

CODEN: ANCHAM; ISSN: 0003-2700
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The retention mechanism of a weak polar solute, 10 benzodiazepines in reversed phase liquid chromatog., were studied over a wide range of mobile phase compns. The values of enthalpy (ΔH°) and entropy (ΔS°) of transfer from the mobile to the stationary phases were determined The method studied each factor (water fraction Φ in the MeCN (ACN)/H2O mixture and column **temp**.) controlling the retention mechanism. The changes in ΔH° and ΔS° as a function of the H2O fraction Φ in the ACN/H2O mixture were examined These variations are explained using the organization of organic modifier (ACN) in clusters in the ACN/H2O mixture A change in the retention mechanism thus indicated when the ACN/H2O mixture was used instead of the H-bonded mobile phase such as MeOH/H2O. Enthalpy-entropy compensation revealed that the retention mechanism was independent of the H2O fraction Φ but showed that differences between the mol. structures of the benzodiazepines contributed more significantly to changes in the retention process in the MeOH/H2O mixture than in the ACN/H2O mixture

IT **22345-47-7, Tofisopam**
RL: ANT (Analyte); PEP (Physical, engineering or chemical process); PRP (Properties); ANST (Analytical study); PROC (Process)
(retention mechanism of weak polar solutes in reversed phase liquid chromatog.)

RN 22345-47-7 CAPLUS
CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)

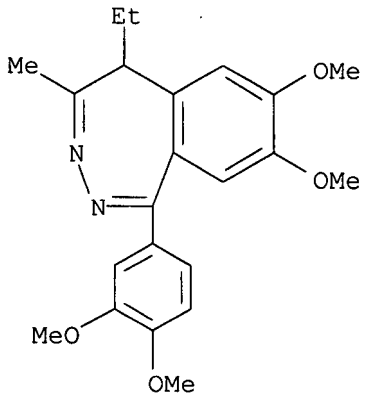


L7 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1978:94763 CAPLUS
DOCUMENT NUMBER: 88:94763
TITLE: Rapid method for the determination of the heat occurring during the compression of pharmaceutical tablets
AUTHOR(S): Kovacs, B.; Toth, Z.; Baumann-Uderszky, Judit; Gyarmati, L.
CORPORATE SOURCE: Pharm. Inst., Semmelweis Med. Univ., Budapest, Hung.
SOURCE: Pharmazeutische Industrie (1977), 39(10), 1010-11
CODEN: PHINAN; ISSN: 0031-711X
DOCUMENT TYPE: Journal
LANGUAGE: German

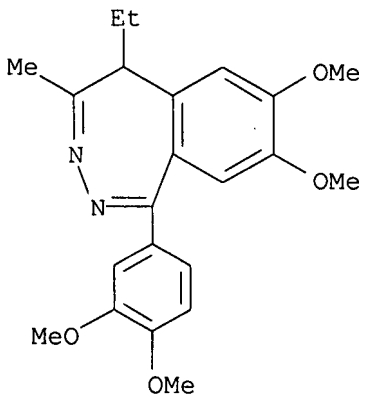
AB A method for determining the amount of heat absorbed by tablets during compression involves calorimetric measurement of the **temp**. rise of a known amount of paraffin oil into which the freshly compressed tablets are poured.

The portable apparatus consists of measuring and reference systems, electrodes, and a digital readout device. The method can be used with tablets of varying weight and composition, produced under differing pressing conditions. The mean deviation in parallel detns. on various tablets was ≤5%.

IT **22345-47-7**
RL: BIOL (Biological study)
(tablets, heat of compression of, determination of)
RN 22345-47-7 CAPLUS
CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



L7 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1975:124585 CAPLUS
DOCUMENT NUMBER: 82:124585
TITLE: Heterocyclic compounds. II. 100-MHz PMR, pulse Fourier transform carbon-13 NMR, and mass spectroscopic studies of 1-(3,4-dimethoxyphenyl)-5-ethyl}-7,8-dimethoxy-4-methyl-5H-2,3-benzodiazepine
AUTHOR(S): Neszmelyi, Andras; Gacs-Baitz, Eszter; Horvath, Gyula; Lang, Tibor; Korosi, Jeno
CORPORATE SOURCE: Inst. Pharmacol. Res., Budapest, Hung.
SOURCE: Chemische Berichte (1974), 107(12), 3894-903
CODEN: CHBEAM; ISSN: 0009-2940
DOCUMENT TYPE: Journal
LANGUAGE: German
GI For diagram(s), see printed CA Issue.
AB NMR and mass spectoscopic studies on the diazepine (I) showed that the enamine 3-H-tautomer did not exist even at high **temp**. and that I had only 2 boat conformations in equilibrium with each other.
IT **22345-47-7**
RL: PRP (Properties)
(conformation of, mass spectrum and NMR in relation to)
RN 22345-47-7 CAPLUS
CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)

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L2            71 S L1 AND 5H
L3            57 S L2 AND 4-METHYL
L4             0 S L3 AND 2-ETHYL

     FILE 'CAPLUS' ENTERED AT 22:35:22 ON 27 SEP 2007
L5           226 S 22345-47-7/RN OR EGYT 341 OR GRANDAXIN OR SERIEL OR TOFISOPAM
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L6            20 S L5 AND (TEMPERATURE OR BODY TEMPERATURE)
L7            20 FOCUS L6 1-

=> s l5 and (hot flash or menopause)
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             45 HOTS
         453013 HOT
                   (HOT OR HOTS)
          59984 FLASH
           4389 FLASHES
          62351 FLASH
                   (FLASH OR FLASHES)
            872 HOT FLASH
                   (HOT(W)FLASH)
          15149 MENOPAUSE
L8            3 L5 AND (HOT FLASH OR MENOPAUSE)

=> d ibib abs 1-3

L8   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2004:995773  CAPLUS
DOCUMENT NUMBER:          141:410971
TITLE:                    A preparation of 2,3-benzodiazepine derivatives,
                          useful as antipyretic agents
INVENTOR(S):              Harris, Herbert W.; Kucharik, Robert F.
PATENT ASSIGNEE(S):       Vela Pharmaceuticals, Inc., USA
SOURCE:                   U.S. Pat. Appl. Publ., 23 pp., Cont.-in-part of U.S.
                          Ser. No. 369,823.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   3
PATENT INFORMATION:
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PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004229866	A1	20041118	US 2004-781422	20040217
US 2004162284	A1	20040819	US 2003-369823	20030219
US 2004224943	A1	20041111	US 2004-827839	20040419
PRIORITY APPLN. INFO.:			US 2003-369823	A2 20030219
			US 2004-781422	A2 20040217

OTHER SOURCE(S): MARPAT 141:410971
GI

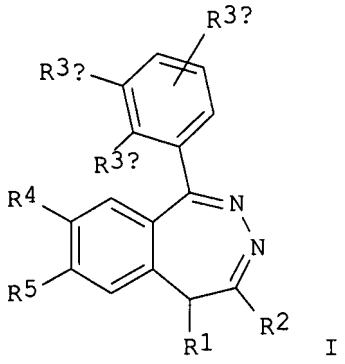
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to a preparation of 2,3-benzodiazepine derivs. of formula I [wherein: R1 is hydrocarbyl or heteroalkyl; R2 is H or hydrocarbyl; R1 and R2 may combine to form a (carbo/hetero)cyclic ring; R3 and R4 are independently selected from OH, SH, NO2, halogen, or S-alkyl, etc.; R5 is substituted phenyl], useful as antipyretic agents. For instance, (S)-2,3-benzodiazepine derivative II was prepared via heterocyclization of diketone III with hydrazine and subsequent resolution The prepared title compds. were tested in stress-induced hypothermia assay. (S)-enantiomer of **tofisopam** showed higher activity than the racemate or the (R)-enantiomer [dose: 64 mg/kg, (S)-**tofisopam**: 33 °C, (R)-**tofisopam**: 35.25 °C, racemate: 33.75 °C].

L8 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:964818 CAPLUS
DOCUMENT NUMBER: 141:410972
TITLE: Preparation of (R)-2,3-benzodiazepine derivatives and method of lowering body temperature with them
INVENTOR(S): Leventer, Steven M.; Kucharik, Robert F.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 22 pp., Cont.-in-part of U.S. Ser. No. 781,422.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004224943	A1	20041111	US 2004-827839	20040419
US 2004162284	A1	20040819	US 2003-369823	20030219
US 2004229866	A1	20041118	US 2004-781422	20040217
PRIORITY APPLN. INFO.:			US 2003-369823	A2 20030219
			US 2004-781422	A2 20040217

OTHER SOURCE(S): MARPAT 141:410972
GI



I

AB An (R)-2,3-benzodiazepine of formula (I) [R1 = C1-7 hydrocarbyl, C2-6 heteroalkyl; R2 = H, C1-7 hydrocarbyl; or R1 and R2 may combine to form a carbocyclic or heterocyclic 5- or 6-membered ring; R3a, R3b, R3c = H, -O-C1-7 hydrocarbyl, OH, -OC(O)-C1-6 alkyl, -OC(O)O-C1-7 hydrocarbyl, SH, -S-C1-3 alkyl, NH2, -NH-C1-6 alkyl, -N(C1-6 alkyl)2, -NH(:O)-C1-6 alkyl, NO2, halogen; provided at least one of R3a, R3b and R3c is other than H; R4, R5 = -O-C1-7 hydrocarbyl, OH, -OC(O)-C1-6 alkyl, -OC(O)O-C1-7 hydrocarbyl, SH, -S-C1-3 alkyl, NH2, -NH-C1-6 alkyl, -N(C1-6 alkyl)2, -NH(:O)-C1-6 alkyl, NO2, halo; or R4 and R5 may combine to form a 5-, 6- or 7-membered heterocyclic ring], substantially free from the corresponding (S)-enantiomer thereof with respect to the absolute conformation at the 5-position of the benzodiazepine ring, is administered to lower the body temperature of an individual. More specifically, the administered compound is (R)-**tofisopam**, or a pharmaceutically-acceptable salt thereof and said individual is afflicted with a disorder associated with an elevated body temperature such as fever, malignant hyperthermia, serotonin syndrome, or **hot flashes** during **menopause** or perimenopause or occurred as side effects of drug therapy or subsequent to the removal of estrogen-producing tissue. Furthermore said individual is afflicted with a disorder such as cerebral ischemia or stroke wherein therapeutic benefit is achieved by lowering of the body temperature to a level below the normal body temperature Thus, 4.41 g (10 mmol) 1-(3,4-dimethoxyphenyl)-3-methyl-4-ethyl-6,7-dimethoxyisobenzopyrylium chloride hydrochloride was dissolved in methanol (35 mL) at 40°, cooled to 20-25°, treated with a solution of hydrazine hydrate (0.75 g, 15 mmol)in 5 mL methanol, and allowed to reaction. The reaction was monitored by HPLC and when complete, was evaporated to dryness. The residue is triturated with cold water (3 mL), filtered, and dried to yield crude (RS)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine (racemic **tofisopam**). Racemic **tofisopam** was resolved by chiral chromatog. using a semipreparative Chirobiotic V column (ASTEC, Whippany, New Jersey) and Me tert-Bu ether/MeCN as the eluent to give (R)-**tofisopam** and (S)-**tofisopam**. In a stress induced hyperthermia assay using mice, racemic **tofisopam** demonstrated activity in lowering the core body temperature (S)-**tofisopam** was more active than either the racemate or the (R)-enantiomer. However, the (R)-enantiomer showed greater tolerability compared with either the racemate or the (S)-enantiomer. For example, the mice treated with the (R)-enantiomer showed less sedation, abnormal gait, or ptosis, decreased muscle tone, decreased lacrimation, or decreased reactivity to touch compared with either (S)-enantiomer or the racemate.

L8 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:681397 CAPLUS
DOCUMENT NUMBER: 141:167829
TITLE: Method of lowering body temperature with (S)-

tofisopam

INVENTOR(S): Harris, Herbert W.; Kucharik, Robert F.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 14 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004162284	A1	20040819	US 2003-369823	20030219
WO 2004073638	A2	20040902	WO 2004-US4726	20040217
WO 2004073638	A3	20050113		

W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004229866	A1	20041118	US 2004-781422	20040217
US 2004224943	A1	20041111	US 2004-827839	20040419
PRIORITY APPLN. INFO.:			US 2003-369823 A	20030219
			US 2004-781422 A2	20040217

AB (S)-**Tofisopam**, substantially isolated from the corresponding (R)-enantiomer of **tofisopam**, is administered to lower the body temperature of an individual.

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=> file medline biosis embase
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   143.59     306.70

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                   -17.94     -17.94

FILE 'MEDLINE' ENTERED AT 22:41:13 ON 27 SEP 2007

FILE 'BIOSIS' ENTERED AT 22:41:13 ON 27 SEP 2007
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FILE 'EMBASE' ENTERED AT 22:41:13 ON 27 SEP 2007
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=> s 22345-47-7/rn or egyt 341 or grandaxin or seriel or tofisopam
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
L9          481 22345-47-7/RN OR EGYT 341 OR GRANDAXIN OR SERIEL OR TOFISOPAM

=> d his

     (FILE 'HOME' ENTERED AT 22:31:56 ON 27 SEP 2007)

     FILE 'REGISTRY' ENTERED AT 22:32:09 ON 27 SEP 2007
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L1          135 S BENZODIAZEPINE AND DIMETHOXY AND ETHYL AND METHYL AND DIMETHO
L2           71 S L1 AND 5H
L3           57 S L2 AND 4-METHYL
L4            0 S L3 AND 2-ETHYL

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L5          226 S 22345-47-7/RN OR EGYT 341 OR GRANDAXIN OR SERIEL OR TOFISOPAM
                E TEMPERATURE+ALL/CT
L6           20 S L5 AND (TEMPERATURE OR BODY TEMPERATURE)
L7           20 FOCUS L6 1-
                E HOT FLASH+ALL/CT
                E MENOPAUSE+ALL/CT
L8            3 S L5 AND (HOT FLASH OR MENOPAUSE)

     FILE 'MEDLINE, BIOSIS, EMBASE' ENTERED AT 22:41:13 ON 27 SEP 2007
L9          481 S 22345-47-7/RN OR EGYT 341 OR GRANDAXIN OR SERIEL OR TOFISOPAM

=> s l9 and (temperature or body temperature or hot flash or menopause or feeling
hot or thermo?)
L10          22 L9 AND (TEMPERATURE OR BODY TEMPERATURE OR HOT FLASH OR MENOPAU
                SE OR FEELING HOT OR THERMO?)

=> focu
PROCESSING COMPLETED FOR L10
L11          22 FOCUS L10 1-

=> d ibib abs 1-22

L11  ANSWER 1 OF 22  BIOSIS  COPYRIGHT (c) 2007 The Thomson Corporation  on STN
ACCESSION NUMBER:    2004:196728  BIOSIS
DOCUMENT NUMBER:     PREV200400197287
TITLE:               Effects of S - tofisopam on physiological
                     measurements in the ovariectomized rodent model of
                     menopause.
AUTHOR(S):           Harris, H. [Reprint Author]; Leventer, S. M. [Reprint
                     Author]; Kucharik, R. [Reprint Author]; Gidner, J. [Reprint
                     Author]; Speicher, B. [Reprint Author]; Keogh, J. C.
                     [Reprint Author]; Galbraith, K. [Reprint Author]; Ye, N.
                     [Reprint Author]; Sarnyai, Z.; Florino, L.; Klitenick, M.;
                     Keim, K. L. [Reprint Author]
CORPORATE SOURCE:    Vela Pharm, Lawrenceville, NJ, USA
SOURCE:              Society for Neuroscience Abstract Viewer and Itinerary
                     Planner, (2003) Vol. 2003, pp. Abstract No. 281.14.
                     http://sfn.scholarone.com. e-file.
                     Meeting Info.: 33rd Annual Meeting of the Society of
                     Neuroscience. New Orleans, LA, USA. November 08-12, 2003.
                     Society of Neuroscience.
DOCUMENT TYPE:       Conference; (Meeting)
                     Conference; Abstract; (Meeting Abstract)
LANGUAGE:            English
ENTRY DATE:          Entered STN: 14 Apr 2004
                     Last Updated on STN: 14 Apr 2004
AB   Tofisopam is a racemic, atypical, 2,3-benzodiazepine marketed in
     more than 15 countries outside of the United States.  Although
     tofisopam was initially approved for use in anxiety disorders, the
     compound has since been found useful for the treatment of vasomotor and
     other symptoms associated with menopause.  The identification of
     a chiral center in the molecule led to the purification of the two
     enantiomers of tofisopam, R-and S-tofisopam.  The
     objective of the present study was to determine the effects of S-
     tofisopam on skin temperature in ovariectomized mice, a
     putative animal model of menopausal hot flashes
     .Female, ovariectomized 129SVEV (OVX) mice (Taconic, Germantown, NY) were
     received at 6 weeks of age.  Consistent with the published literature on
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ovariectomized animals, skin **temperature** measurements obtained over the course of 7 weeks following surgery indicated a steady rise that reached a maximum increase of approximately 2degreeC. Seven weeks after surgery, S-**tofisopam** was administered by intraperitoneal injection, producing a statistically significant drop in skin **temperature** 75 minutes after administration (1.35degreeC, p=0.001). Further behavioral and neuroendocrine studies employing OVX mice are underway.These findings are consistent with the published literature indicating that racemic **tofisopam** has clinical utility in treating vasomotor symptoms associated with **menopause** . In addition, these data indicate that S-**tofisopam** possesses the potential for clinical utility in the treatment of symptoms of **menopause** and possibly other disorders.

L11 ANSWER 2 OF 22 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2006429873 EMBASE
TITLE: Method validation and determination of enantiomers and conformers in **tofisopam** drug substances and drug products by chiral high-performance liquid chromatography and kinetic and **thermodynamic** study of the interconversion of the conformers.
AUTHOR: Hu M.; He P.; Chen Y.; Carr G.; Guo J.; Ye N.
CORPORATE SOURCE: M. Hu, Patheon Inc., 2100 Syntex Court, Mississauga, Ont. L5N 7K9, Canada. mougang.hu@patheon.com
SOURCE: Journal of Chromatography A, (29 Sep 2006) Vol. 1129, No. 1, pp. 47-53.
Refs: 16
ISSN: 0021-9673 CODEN: JCRAEY
PUBLISHER IDENT.: S 0021-9673(06)01250-7
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 3 Oct 2006
Last Updated on STN: 3 Oct 2006

AB 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine (**tofisopam**) contains one chiral center, so two enantiomeric forms exist. The ring system of **tofisopam** possesses two sterically stable boat structures, leading to two distinct conformers for each enantiomer. A method was developed for the separation of these enantiomers and conformers in the drug substances and drug products. Separation was achieved with a separation factor of at least 3.9 for any adjacent peaks. Validation of the method challenged linearity, limit of detection, limit of quantification, specificity, accuracy, repeatability, intermediate precision, robustness, and stability of standard and sample solutions, and all validation results met the acceptance criteria. A study of accuracy at 80%, 100%, and 120% levels gave recoveries of 100 ± 1%. The RSD of six sample injections for repeatability was less than 0.5%. The detection limit of **tofisopam** enantiomer was as low as 0.12 μg/mL. The kinetics and **thermodynamics** of the interconversion of **tofisopam** conformers were also investigated, and the kinetic and equilibrium constants of the interconversion process were determined at 15 °C, 25 °C, and 35 °C. .COPYRGT. 2006 Elsevier B.V. All rights reserved.

L11 ANSWER 3 OF 22 MEDLINE on STN

ACCESSION NUMBER: 2006537854 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16844130
TITLE: Method validation and determination of enantiomers and

conformers in **tofisopam** drug substances and drug products by chiral high-performance liquid chromatography and kinetic and **thermodynamic** study of the interconversion of the conformers.

AUTHOR: Hu Mougang; He Ping; Chen Yong; Carr Geoff; Guo Junan; Ye Naidong

CORPORATE SOURCE: Patheon Inc., Mississauga, Ont. L5N 7K9, Canada.. mougang.hu@patheon.com

SOURCE: Journal of chromatography. A, (2006 Sep 29) Vol. 1129, No. 1, pp. 47-53. Electronic Publication: 2006-07-17. Journal code: 9318488. ISSN: 0021-9673.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200611

ENTRY DATE: Entered STN: 12 Sep 2006
Last Updated on STN: 19 Dec 2006
Entered Medline: 22 Nov 2006

AB 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine (**tofisopam**) contains one chiral center, so two enantiomeric forms exist. The ring system of **tofisopam** possesses two sterically stable boat structures, leading to two distinct conformers for each enantiomer. A method was developed for the separation of these enantiomers and conformers in the drug substances and drug products. Separation was achieved with a separation factor of at least 3.9 for any adjacent peaks. Validation of the method challenged linearity, limit of detection, limit of quantification, specificity, accuracy, repeatability, intermediate precision, robustness, and stability of standard and sample solutions, and all validation results met the acceptance criteria. A study of accuracy at 80%, 100%, and 120% levels gave recoveries of 100 +/- 1%. The RSD of six sample injections for repeatability was less than 0.5%. The detection limit of **tofisopam** enantiomer was as low as 0.12 microg/mL. The kinetics and **thermodynamics** of the interconversion of **tofisopam** conformers were also investigated, and the kinetic and equilibrium constants of the interconversion process were determined at 15 degrees C, 25 degrees C, and 35 degrees C.

L11 ANSWER 4 OF 22 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 2007:14827 BIOSIS

DOCUMENT NUMBER: PREV200700015228

TITLE: Method validation and determination of enantiomers and conformers in **tofisopam** drug substances and drug products by chiral high-performance liquid chromatography and kinetic and **thermodynamic** study of the interconversion of the conformers.

AUTHOR(S): Hu, Mougang; He, Ping; Chen, Yong; Carr, Geoff; Guo, Junan [Reprint Author]; Ye, Naidong

CORPORATE SOURCE: Patheon Inc, 2100 Syntex Court, Mississauga, ON L5N 7K9, Canada
mougan.hu@patheon.com; junan.guo@patheon.com

SOURCE: Journal of Chromatography A, (SEP 29 2006) Vol. 1129, No. 1, pp. 47-53.
CODEN: JOCRAM. ISSN: 0021-9673.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 20 Dec 2006
Last Updated on STN: 20 Dec 2006

AB 1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine (**tofisopam**) contains one chiral center, so two enantiomeric forms exist. The ring system of **tofisopam** possesses two sterically stable boat structures, leading to two distinct conformers for each enantiomer. A method was developed for the separation

of these enantiomers and conformers in the drug substances and drug products. Separation was achieved with a separation factor of at least 3.9 for any adjacent peaks. Validation of the method challenged linearity, limit of detection, limit of quantification, specificity, accuracy, repeatability, intermediate precision, robustness, and stability of standard and sample solutions, and all validation results met the acceptance criteria. A study of accuracy at 80%, 100%, and 120% levels gave recoveries of 100 +/- 1%. The RSD of six sample injections for repeatability was less than 0.5%. The detection limit of **tofisopam** enantiomer was as low as 0.12 mu g/mL. The kinetics and **thermodynamics** of the interconversion of **tofisopam** conformers were also investigated, and the kinetic and equilibrium constants of the interconversion process were determined at 15 degrees C, 25 degrees C, and 35 degrees C.

L11 ANSWER 5 OF 22 EMBASE

ACCESSION NUMBER: 1995252142 EMBASE
TITLE: Marked differences between acetonitrile/water and methanol/water mobile phase systems on the **thermodynamic** behavior of benzodiazepines in reversed phase liquid chromatography.
AUTHOR: Guillaume Y.; Guinchard C.
CORPORATE SOURCE: Y. Guillaume, Laboratoire de Chimie Analytique, Fac. Sciences Medicales/Pharmaceut., Place St. Jacques, 25030 Besancon Cedex, France
SOURCE: Chromatographia, (1995) Vol. 41, No. 1-2, pp. 84-87. ISSN: 0009-5893 CODEN: CHRGB7
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 032 Psychiatry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Sep 1995
Last Updated on STN: 12 Sep 1995

AB Two different methods were used to determine the separation factor α at different **temperatures** and the Gibbs-Helmholtz parameters (Δ(ΔH), Δ(ΔS)) of two adjacent benzodiazepines on a chromatogram were obtained from plots of lnα versus 1/T. We first studied each factor (fraction of water Φ in the ACN/water mixture and column **temperature** T), which controls the retention mechanism, and then we examined the simultaneous variation of all these factors. The changes in Δ(ΔH) and Δ(ΔS) in relation to a volume fraction of water Φ in an ACN/water mixture were examined. In the ACN/water system, Δ(H) was fairly constant in the acetonitrile region of Φ 0.52 and appears to be a roughly linear function of Φ for Φ 0.52. In this system Δ(ΔS) is approximately a parabolic function of Φ with an optimum at Φ .simeq. 0.52. The retention mechanism of ten benzodiazepines was found to be significantly different in the methanol/water and ACN/water mixtures. The separation optimization of these ten benzodiazepines was then considered. A fraction of water of 0.43 in the ACN/water mixture and a column **temperature** of 44°C gave the most efficient separation conditions in the ACN/water mixture.

L11 ANSWER 6 OF 22 EMBASE

ACCESSION NUMBER: 1983207312 EMBASE
TITLE: **Tofisopam**, a new 2,3-benzodiazepine. Inhibition of changes induced by stress loading and hypothalamic stimulation.
AUTHOR: Yamaguchi K.; Suzuki K.; Niho T.; et. al.

CORPORATE SOURCE: Fuji Cent. Res. Lab., Mochida Pharm. Co. Ltd., Gotemba, Shizuoka 412, Japan
SOURCE: Canadian Journal of Physiology and Pharmacology, (1983) Vol. 61, No. 6, pp. 619-625.
ISSN: 0008-4212 CODEN: CJPPA3
COUNTRY: Canada
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: French
ENTRY DATE: Entered STN: 9 Dec 1991
Last Updated on STN: 9 Dec 1991

AB Effects of **tofisopam**, a new 2,3-benzodiazepine compound, were investigated on the following gastric ulceration, induced by water-immersion stress in normal rats and by immobilization stress in olfactory-bulbectomized (OB) rats; and propulsion of the small intestine caused by water-immersion stress in rats and autonomic responses to electrical stimulation of the hypothalamus in rabbits. In the latter, the results were compared with those of diazepam and γ-oryzanol. **Tofisopam** (30 and 100 mg/kg, po) significantly inhibited the gastric ulceration induced by water-immersion stress in normal rats in a dose-dependent manner. Immobilization-stress loading increased the incidence and average index of gastric ulceration in OB rats, compared with nonstressed rats. **Tofisopam** (100 mg/kg, po) significantly inhibited the gastric ulceration induced by stress loading in OB rats. Water-immersion stress loading induced a significant increase in intestinal propulsion in rats. This increase was reversed to control levels by **tofisopam** (100 mg/kg, po). **Tofisopam** (1.0 mg/kg, iv, or 0.1 mg/kg by intracerebrospinal injection) inhibited the constriction of ear microvessels, the decrease in earlobe **temperature**, and mydriasis induced by electrical stimulation of the medial hypothalamic area in rabbits. However, diazepam and γ-oryzanol failed to inhibit the autonomic responses to medial hypothalamic stimulation. From these results, it can be concluded that **tofisopam** restores the autonomic abnormality induced by stress loading possibly via intervention in the central autonomic area, i.e., the hypothalamus, by an action different from that of diazepam.

L11 ANSWER 7 OF 22 EMBASE
ACCESSION NUMBER: 1977055898 EMBASE
TITLE: The treatment of climacteric syndrome with tofizopam (**Grandaxin**).
AUTHOR: Csillag M.; Gimes G.; Kiss C.; et. al.
CORPORATE SOURCE: I Dept. Gynaecol., Semmelweis Univ. Med. Sch., Budapest, Hungary
SOURCE: Therapia Hungarica, (1975) Vol. 23, No. 4, pp. 164-169.
ISSN: 0133-3909 CODEN: THHUAF
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 010 Obstetrics and Gynecology
020 Gerontology and Geriatrics
030 Clinical and Experimental Pharmacology
032 Psychiatry
037 Drug Literature Index
LANGUAGE: English

AB 172 climacteric patients were treated with **Grandaxin**. According to the results of examinations **Grandaxin** proved to be of clinical value in the treatment of climacteric syndrome. In the majority of cases (with complaints of mild, resp. moderate intensity) it decreased or controlled the psychic and neurovegetative symptoms when given as single agent. The drug ameliorates the general condition of the patients by moderating the majority of complaints, and by increasing the tolerance

of symptoms as a consequence or by relieving them. The application of hormone therapy is indicated only in severe cases; in these cases **Grandaxin** prolongs the hormone effect and reduces the requirement for frequent hormone administration. The safety of **Grandaxin** treatment has to be emphasized. Its great advantage is that it does not influence or only beneficially influences the daily working ability of the patients.

L11 ANSWER 8 OF 22 MEDLINE on STN
ACCESSION NUMBER: 83284617 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6136319
TITLE: **Tofisopam**, a new 2,3-benzodiazepine. Inhibition of changes induced by stress loading and hypothalamic stimulation.
AUTHOR: Yamaguchi K; Suzuki K; Niho T; Shimora M; Ito C; Ohnishi H
SOURCE: Canadian journal of physiology and pharmacology, (1983 Jun) Vol. 61, No. 6, pp. 619-25.
Journal code: 0372712. ISSN: 0008-4212.
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198310
ENTRY DATE: Entered STN: 19 Mar 1990
Last Updated on STN: 6 Feb 1995
Entered Medline: 21 Oct 1983

AB Effects of **tofisopam**, a new 2,3-benzodiazepine compound, were investigated on the following: gastric ulceration, induced by water-immersion stress in normal rats and by immobilization stress in olfactory-bulbectomized (OB) rats; and propulsion of the small intestine caused by water-immersion stress in rats and autonomic responses to electrical stimulation of the hypothalamus in rabbits. In the latter, the results were compared with those of diazepam and gamma-oryzanol. **Tofisopam** (30 and 100 mg/kg, po) significantly inhibited the gastric ulceration induced by water-immersion stress in normal rats in a dose-dependent manner. Immobilization-stress loading increased the incidence and average index of gastric ulceration in OB rats, compared with nonstressed rats. **Tofisopam** (100 mg/kg, po) significantly inhibited the gastric ulceration induced by stress loading in OB rats. Water-immersion stress loading induced a significant increase in intestinal propulsion in rats. This increase was reversed to control levels by **tofisopam** (100 mg/kg, po). **Tofisopam** (1.0 mg/kg, iv, or 0.1 mg/kg by intracerebrospinal injection) inhibited the constriction of ear microvessels, the decrease in earlobe **temperature**, and mydriasis induced by electrical stimulation of the medial hypothalamic area in rabbits. However, diazepam and gamma-oryzanol failed to inhibit the autonomic responses to medial hypothalamic stimulation. From these results, it can be concluded that **tofisopam** restores the autonomic abnormality induced by stress loading possibly via intervention in the central autonomic area, i.e., the hypothalamus, by an action different from that of diazepam.

L11 ANSWER 9 OF 22 MEDLINE on STN
ACCESSION NUMBER: 82118267 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7327446
TITLE: Effects of **tofisopam** on the physiological changes induced by stress loading and hypothalamic stimulation (author's transl).
AUTHOR: Ohnishi H; Ito C; Suzuki K; Niho T; Shimora M; Yamaguchi K
SOURCE: Nippon yakurigaku zasshi. Folia pharmacologica Japonica, (1981 Sep) Vol. 78, No. 3, pp. 139-44.
Journal code: 0420550. ISSN: 0015-5691.
Report No.: NASA-82118267.
PUB. COUNTRY: Japan

DOCUMENT TYPE: (ENGLISH ABSTRACT)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 198204
ENTRY DATE: Entered STN: 17 Mar 1990
Last Updated on STN: 17 Mar 1990
Entered Medline: 12 Apr 1982

AB Effects of **tofisopam** on the gastric ulceration induced by immobilization stress in olfactory-bulbectomized rats, propulsion of the small intestine caused by water immersion-stress in rats and autonomic responses to electrical stimulation of the hypothalamus in rabbits were investigated. Immobilization stress loading of 16.5 hours each for 10 days caused the augmentation of incidence and average index of gastric ulceration in olfactory-bulbectomized rats, compared with non-treated rats. **Tofisopam** 100 mg/kg, p.o. significantly inhibited the gastric ulceration in olfactory-bulbectomized rats. Water immersion-stress loading for 2 hours caused a significant increase in propulsion of the small intestine in rats. This increase was reversed to control levels after the oral administration of **tofisopam** in a dose of 100 mg/kg. **Tofisopam** at dose of 1 mg/kg i.v. inhibited the contraction of ear microvessels, the decrease in earlobe **temperature** and the mydriasis induced by electrical stimulation of the medial hypothalamic area in rabbits, Moreover, these inhibitions were also shown by the intra-cerebrospinal injection of **tofisopam** at a dose of 0.1 mg/kg. From these results, it is concluded that **tofisopam** could restore the autonomic abnormality induced by stress-loading and exerts such effects by acting on the hypothalamus, an area of the brain, which regulates autonomic nervous functions.

L11 ANSWER 10 OF 22 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 1984:181073 BIOSIS
DOCUMENT NUMBER: PREV198477014057; BA77:14057
TITLE: **TOFISOPAM** A NEW 2 3 BENZODIAZEPINE INHIBITION OF CHANGES INDUCED BY STRESS LOADING AND HYPOTHALAMIC STIMULATION.
AUTHOR(S): YUAMAGUCHI K [Reprint author]; SUZUKI K; NIHO T; SHIMORA M; ITO C; OHNISHI H
CORPORATE SOURCE: FUJI CENTRAL RESEARCH LABORATORY, MOCHIDA PHARMACEUTICAL CO, LTD, 722, JIMBA-AZA-UENOHARA, GOTEMBA, SHIZUOKA 412, JAPAN
SOURCE: Canadian Journal of Physiology and Pharmacology, (1983) Vol. 61, No. 6, pp. 619-625.
CODEN: CJPPA3. ISSN: 0008-4212.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH

AB Effects of **tofisopam**, a new 2,3-benzodiazepine compound, were investigated on gastric ulceration, induced by water-immersion stress in normal rats and by immobilization stress in olfactory-bulbectomized (OB) rats; and propulsion of the small intestine caused by water-immersion stress in rats and autonomic responses to electrical stimulation of the hypothalamus in rabbits. In the latter, the results were compared with those of diazepam and y-oryzanol. **Tofisopam** (30 and 100 mg/kg, p.o. [orally]) significantly inhibited the gastric ulceration induced by water-immersion stress in normal rats in a dose-dependent manner. Immobilization-stress loading increased the incidence and average index of gastric ulceration in OB rats, compared with nonstressed rats. **Tofisopam** (100 mg/kg, po) significantly inhibited the gastric ulceration induced by stress loading in OB rats. Water-immersion stress loading induced a significant increase in intestinal propulsion in rats. This increase was reversed to control levels by **tofisopam** (100 mg/kg, po). **Tofisopam** (1.0 mg/kg, i.v. or 0.1 mg/kg by

intracerebrospinal injection) inhibited the constriction of ear microvessels, the decrease in earlobe **temperature** and mydriasis induced by electrical stimulation of the medial hypothalamis area in rabbits. Diazepam and γ-oryzanol failed to inhibit the autonomic responses to medial hypothalamic stimulation. **Tofisopam** evidently restores the autonomic abnormality induced by stress loading possibly via intervention in the central autonomic area, i.e., the hypothalamus, by an action different from that of diazepam.

L11 ANSWER 11 OF 22 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 1982:225751 BIOSIS
DOCUMENT NUMBER: PREV198273085735; BA73:85735
TITLE: EFFECTS OF **TOFISOPAM** ON THE PHYSIOLOGICAL CHANGES INDUCED BY STRESS LOADING AND HYPOTHALAMIC STIMULATION.
AUTHOR(S): OHNISHI H [Reprint author]; ITO C; SUZUKI K; NIHO T; SHIMORA M; YAMAGUCHI K
CORPORATE SOURCE: RESEARCH LAB OF PHARMACOLOGY, MOCHIDA PHARMACEUTICAL CO LTD, KAMIYA 1-1-1, KITA-KU, TOKYO 115, JAPAN
SOURCE: Folia Pharmacologica Japonica, (1981) Vol. 78, No. 3, pp. 139-144.
CODEN: NYKZAU. ISSN: 0015-5691.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: JAPANESE

AB Effects of **tofisopam** on gastric ulceration induced by immobilization stress in olfactory-bulbectomized rats, propulsion of the small intestine caused by water immersion-stress in rats, and autonomic responses to electrical stimulation of the hypothalamus in rabbits were investigated. Immobilization stress loading of 16.5 h each for 10 days caused the augmentation of incidence and average index of gastric ulceration in olfactory-bulbectomized rats, compared with non-treated rats. **Tofisopam**, 100 mg/kg, orally, significantly inhibited the gastric ulceration in olfactory-bulbectomized rats. Water immersion-stress loading for 2 h caused a significant increase in propulsion of the small intestine in rats. This increase was reversed to control levels after the oral administration of 100 mg/kg **tofisopam**. **Tofisopam**, 1 mg/kg i.v., inhibited the contraction of ear microvessels, the decrease in earlobe **temperature** and the mydriasis induced by electrical stimulation of the medial hypothalamic area in rabbits. These inhibitions were also shown by the intra-cerebrospinal injection of **tofisopam** at 0.1 mg/kg. Apparently, **tofisopam** could restore the autonomic abnormality induced by stress-loading, and exerts such efects by acting on the hypothalamus, which regulates autonomic nervous functions.

L11 ANSWER 12 OF 22 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 1999:334551 BIOSIS
DOCUMENT NUMBER: PREV199900334551
TITLE: Influence of ionic strength and organic modifier on performance in capillary electrochromatography on phenyl silica stationary phase.
AUTHOR(S): Cahours, X.; Morin, Ph. [Reprint author]; Dreux, M.
CORPORATE SOURCE: Institut de Chimie Organique et Analytique, CNRS UPRES-A 6005, 45 067, Orleans Cedex 2, France
SOURCE: Journal of Chromatography A, (June 11, 1999) Vol. 845, No. 1-2, pp. 203-216. print.
CODEN: JOCRAM. ISSN: 0021-9673.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Aug 1999
Last Updated on STN: 24 Aug 1999

AB The influence of three physicochemical parameters (**temperature**,

ionic strength and organic modifier content of the hydro-organic buffer) upon electrophoretic (electroosmotic flow, EOF, chromatographic (retention factor) and separation (retention time, peak efficiency) performances has been carefully investigated in capillary electrochromatography (CEC) on a phenyl bonded silica column. Five benzodiazepines (diazepam, lorazepam, oxazepam, temazepam, **tofisopam**) have been selected as test solutes. From our CEC results, an increase of the organic modifier content induces an increase of EOF and peak efficiency and a decrease of retention factor. Concerning the ionic strength parameter, an increase of the ionic strength undergoes a decrease of EOF and retention factor and an increase of peak efficiency. Finally, higher **temperature** of the column involves an increase of EOF and peak efficiency and a decrease of retention factor. So, the modification of ionic strength and **temperature** in CEC canmainly be interpreted as a CE-like behavior at the opposite of organic modifier content which acts as a LC-like behavior. At last, the CEC separation of these benzodiazepines has been achieved in 18 min. using TriscntdotHCl (pH 8)-acetonitrile (60:40) mixture, ionic strength 5 mM as mobile phase, and a 3 mum phenyl-bonded silica as stationary phase. High peak efficiencies (200 000 theoretical plates/meter) and resolutions of 1.5 are easily obtained.

L11 ANSWER 13 OF 22 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1999234493 EMBASE
TITLE: Influence of ionic strength and organic modifier on performance in capillary electrochromatography on phenyl silica stationary phase.
AUTHOR: Cahours X.; Morin Ph.; Dreux M.
CORPORATE SOURCE: Ph. Morin, Inst. Chimie Organique/Analytique, CNRS UPRES-A 6005, B.P. 6759, 45067 Orleans Cedex 2, France
SOURCE: Journal of Chromatography A, (11 Jun 1999) Vol. 845, No. 1-2, pp. 203-216.
Refs: 42
ISSN: 0021-9673 CODEN: JCRAEY
PUBLISHER IDENT.: S 0021-9673(99)00007-2
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Conference Article; (Conference paper)
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 27 Jul 1999
Last Updated on STN: 27 Jul 1999

AB The influence of three physicochemical parameters (**temperature**, ionic strength and organic modifier content of the hydro-organic buffer) upon electrophoretic (electroosmotic flow, EOF, chromatographic (retention factor) and separation (retention time, peak efficiency) performances has been carefully investigated in capillary electrochromatography (CEC) on a phenyl bonded silica column. Five benzodiazepines (diazepam, lorazepam, oxazepam, temazepam, **tofisopam**) have been selected as test solutes.From our CEC results, an increase of the organic modifier content induces an increase of EOF and peak efficiency and a decrease of retention factor. Concerning the ionic strength parameter, an increase of the ionic strength undergoes a decrease of EOF and retention factor and an increase of peak efficiency. Finally, higher **temperature** of the column involves an increase of EOF and peak efficiency and a decrease of retention factor. So, the modification of ionic strength and **temperature** in CEC can mainly be interpreted as a CE-like behavior at the opposite of organic modifier content which acts as a LC-like behavior.At last, the CEC separation of these benzodiazepines has been achieved in 18 min, using Tris.HCl (pH 8)-acetonitrile (60:40) mixture, ionic strength 5 mM as mobile phase, and a 3 μm phenyl-bonded silica as stationary phase. High peak efficiencies (200 000 theoretical plates/meter) and resolutions of 1.5 are easily obtained. Copyright (C)

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ACCESSION NUMBER: 1993309732 EMBASE
TITLE: Optimizing mobile phase composition, its flow rate and column **temperature** in HPLC using an experimental design assisted with a simplex method.
AUTHOR: Guillaume Y.; Guinchard C.
CORPORATE SOURCE: Y. Guillaume, Laboratore de Chimie Analytique, UFR des Scis. Medicales/Pharmaceut., Place St. Jacques, Besancon, France
SOURCE: Journal of Liquid Chromatography, (1993) Vol. 16, No. 16, pp. 3457-3470.
Refs: 14
ISSN: 0148-3919 CODEN: JLCHD8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
032 Psychiatry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 21 Nov 1993
Last Updated on STN: 21 Nov 1993

AB In this work, a rapid procedure to separate ten compounds in high performance liquid chromatography is presented. The use of an experimental design assisted with a simplex method is proposed to separate these compounds with only thirteen chromatographic analyses to select the mobile phase composition, its flow rate and the column **temperature**. A flow rate of 0.77 ml/min with a percentage of methanol of 49.95% in the mixture methanol-water and a column **temperature** of 51.62°C gave the most efficient separation conditions.

L11 ANSWER 15 OF 22 MEDLINE on STN

ACCESSION NUMBER: 93297300 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8517164
TITLE: [Additional data from the NMR investigation of tofizopam]. Adatok a tofizopam NMR spektroszkopiai vizsgalatahoz.
AUTHOR: Kovesdi I; Ujszaszy K
CORPORATE SOURCE: EGIS Gyogyszergyar Rt., Budapest.
SOURCE: Acta pharmaceutica Hungarica, (1993 Mar) Vol. 63, No. 2, pp. 53-6.
Journal code: 0414322. ISSN: 0001-6659.
PUB. COUNTRY: Hungary
DOCUMENT TYPE: (ENGLISH ABSTRACT)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Hungarian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199307
ENTRY DATE: Entered STN: 6 Aug 1993
Last Updated on STN: 6 Aug 1993
Entered Medline: 22 Jul 1993

AB The seven-membered ring of Tofizopam exists in two stable conformations in solutions. Separately detectable (Et)Me triplets of the conformers offered us a way for quantitative determination of conformer ratios. **Temperature** dependence of free enthalpy of conformers were calculated from the measured conformer ratios in different **temperatures**. Entropy component of the free enthalpy proved to be 35% of the whole at 36 degrees C. Half period of attaining equilibrium ratio of conformers was 2 hours at 36 degrees C.

L11 ANSWER 16 OF 22 MEDLINE on STN

ACCESSION NUMBER: 90272918 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1971957
TITLE: Pharmacological validation of a novel animal model of anticipatory anxiety in mice.
AUTHOR: Lecci A; Borsini F; Volterra G; Meli A
CORPORATE SOURCE: A. Menarini Pharmaceuticals, Pharmacological Research Department, Firenze, Italy.
SOURCE: Psychopharmacology, (1990) Vol. 101, No. 2, pp. 255-61. Journal code: 7608025. ISSN: 0033-3158.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199007
ENTRY DATE: Entered STN: 10 Aug 1990
Last Updated on STN: 6 Feb 1995
Entered Medline: 12 Jul 1990

AB The current study investigates the action of anxiolytics, antidepressants, neuroleptics, antipyretics, muscle relaxants, antihypertensives and naloxone in a novel animal model of anxiety, based on the evidence that mice removed last from their cage develop hyperthermia (stress-induced hyperthermia, SIH) when compared to those removed first. Alprazolam (0.15-0.6 mg/kg), chlordiazepoxide (25 mg/kg), estazolam (1 mg/kg), phenobarbital (20 mg/kg), ethanol (2 and 4 g/kg), buspirone (5 and 10 mg/kg) and prazosin (1 and 2 mg/kg), as well as repeatedly administered diazepam (5 mg/kg), inhibited SIH. In contrast, **tofisopam** (12.5-200 mg/kg), desipramine (15 and 30 mg/kg), amitriptyline (10 mg/kg), fluoxetine (10 and 20 mg/kg), tranylcypromine (5 and 10 mg/kg), chlorpromazine (1 and 2 mg/kg), clozapine (2 and 4 mg/kg), pimozide (0.5 and 1 mg/kg), l-sulpiride (15 and 30 mg/kg), l-propranolol (5 and 10 mg/kg), acetyl salicylic acid (200 and 400 mg/kg), indomethacin (2.5 and 5 mg/kg), verapamil (2.5 and 5 mg/kg), captopril (25 and 50 mg/kg), dantrolene (10 and 20 mg/kg), mephenesin (300 and 600 mg/kg), d-amphetamine (1 and 4 mg/kg) and naloxone (2.5 and 15 mg/kg) were inactive, as were 10 mg/kg imipramine, amitriptyline and fluoxetine injected every day for 21 days. Reserpine at high doses (1.25 and 2.5 mg/kg) but not at a lower dose (0.62 mg/kg) prevented SIH, but in this case animals showed a behavioural syndrome which could have interfered with the occurrence of the hyperthermia.

L11 ANSWER 17 OF 22 EMBASE
ACCESSION NUMBER: 1994131566 EMBASE
TITLE: Study and optimization of column efficiency in HPLC: Comparison of two methods for separating ten benzodiazepines.
AUTHOR: Gillaume Y.; Guinchard C.
CORPORATE SOURCE: Y. Gillaume, Laboratorie Chimie Analytique, UFR Sci. Medicales/Pharmaceutiques, Place St. Jacques, Besancon, France
SOURCE: Journal of Liquid Chromatography, (1994) Vol. 17, No. 7, pp. 1443-1459.
Refs: 17
ISSN: 0148-3919 CODEN: JLCHD8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 2 Jun 1994
Last Updated on STN: 2 Jun 1994

AB To understand the influence of mobile phase composition, its flow rate and column **temperature** involved in high performance Liquid Chromatography, an experimental design was used. The observed responses were the theoretical plate number, the linear velocity of the mobile phase and a new chromatographic resolution function which provided the most efficient separation of ten compounds as ten benzodiazepines. Optimum conditions obtained were compared with another optimization method.

L11 ANSWER 18 OF 22 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1993125464 EMBASE
TITLE: Additional data to the NMR investigation of **tofisopam**.
AUTHOR: Kovesdi I.; Ujszaszy K.
CORPORATE SOURCE: I. Kovesdi, EGIS Gyogyszergyar Rt., Pf. 100, H-1475 Budapest 10, Hungary
SOURCE: Acta Pharmaceutica Hungarica, (1993) Vol. 63, No. 2, pp. 53-56.
ISSN: 0001-6659 CODEN: APHGAO
COUNTRY: Hungary
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: Hungarian
SUMMARY LANGUAGE: English; Hungarian
ENTRY DATE: Entered STN: 6 Jun 1993
Last Updated on STN: 6 Jun 1993

L11 ANSWER 19 OF 22 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001318058 EMBASE
TITLE: Chiral supercritical fluid chromatography on porous graphitic carbon using commercial dimethyl β-cyclodextrins as mobile phase additive.
AUTHOR: Salvador A.; Herbreteau B.; Dreux M.; Karlsson A.; Gyllenhaal O.
CORPORATE SOURCE: B. Herbreteau, Inst. de Chimie Organique/Analytique, UPRES A CNRS 6005, Universite d'Orleans, BP 6759, F-45067 Orleans Cedex 02, France. bernard.herbreteau@univ-orleans.fr
SOURCE: Journal of Chromatography A, (21 Sep 2001) Vol. 929, No. 1-2, pp. 101-112.
Refs: 62
ISSN: 0021-9673 CODEN: JCRAEY
PUBLISHER IDENT.: S 0021-9673(01)01155-4
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 27 Sep 2001
Last Updated on STN: 27 Sep 2001

AB Using dimethylated-β-cyclodextrin mixtures (MeCD) as chiral selectors in CO(2)-polar modifier mobile phase and porous graphitic carbon as solid-phase, chiral supercritical (or subcritical) fluid chromatography was performed. The adsorbed quantity of MeCD onto the porous graphitic carbon (Hypercarb) was measured for various chiral selector concentrations using the breakthrough method with evaporative light scattering detector. The effects of MeCD concentration in the mobile phase, the nature of the polar modifier, the outlet pressure, the column **temperature** and the nature of the commercial MeCD mixture on the retention and the enantioselectivities were studied. For a given solute, the enantioselectivity is greatly dependent on the commercial MeCD mixture used. The retention mechanism was also studied. From the data, we find

that the dominant mechanism for the chiral discrimination is the diastereoisomeric complexation in the mobile phase. .COPYRGT. 2001 Elsevier Science B.V. All rights reserved.

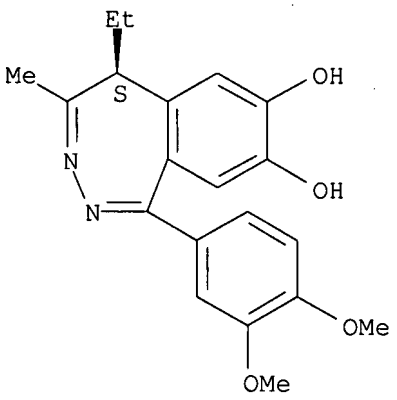
L11 ANSWER 20 OF 22 MEDLINE on STN
ACCESSION NUMBER: 76246699 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7857
TITLE: The treatment of climacteric syndrome with tofizopam (**Grandaxin**).
AUTHOR: Csillag M; Gimes G; Kiss C; Sebo J; Toth F; Toth K; Bolla K
SOURCE: Therapia Hungarica (English edition), (1975) Vol. 23, No. 4, pp. 164-9.
Journal code: 8706535. ISSN: 0133-3909.
PUB. COUNTRY: Hungary
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197609
ENTRY DATE: Entered STN: 13 Mar 1990
Last Updated on STN: 6 Feb 1995
Entered Medline: 25 Sep 1976

L11 ANSWER 21 OF 22 EMBASE
ACCESSION NUMBER: 1997163364 EMBASE
TITLE: A new approach to study benzodiazepine separation and the differences between a methanol/water and acetonitrile/water mixture on column efficiency in liquid chromatography.
AUTHOR: Guillaume Y.; Cavalli E.J.; Peyrin E.; Guinchard C.
CORPORATE SOURCE: Y. Guillaume, Laboratoire Chimie Analytique, Faculte de Medecine Pharmacie, Place Saint-Jacques 25030, Besancon Cedex, France
SOURCE: Journal of Liquid Chromatography and Related Technologies, (1997) Vol. 20, No. 11, pp. 1741-1756.
Refs: 25
ISSN: 1082-6076 CODEN: JLCTFC
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 18 Jun 1997
Last Updated on STN: 18 Jun 1997
AB A chemometric methodology was used to study column efficiency and the separation of 10 benzodiazepines in reversed phase liquid chromatography. New simple mathematical models and the organic modifier (OM) organization of ACN in the water, explained differences on column efficiency observed when ACN is chosen instead of CH(3)OH. A new response function, which takes into account the separation quality and the analysis time, was proposed for the separation optimization. The result, a mobile phase ACN/water (60/4)(V/V), with a flow rate = 1.00 mL/min and a column **temperature** = 47°C were optimum values for a rapid chromatographic separation.

L11 ANSWER 22 OF 22 MEDLINE on STN
ACCESSION NUMBER: 2006264838 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16689340
TITLE: Climacteric disorders.
AUTHOR: Makita Kazuya; Horiguchi Fumi; Aoki Daisuke
CORPORATE SOURCE: Department of Obstetrics and Gynecology, School of Medicine, Keio University.

SOURCE: Nippon rinsho. Japanese journal of clinical medicine, (2006 Apr) Vol. 64 Suppl 4, pp. 394-9. Ref: 14
Journal code: 0420546. ISSN: 0047-1852.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200606
ENTRY DATE: Entered STN: 13 May 2006
Last Updated on STN: 1 Jul 2006
Entered Medline: 30 Jun 2006

Absolute stereochemistry.

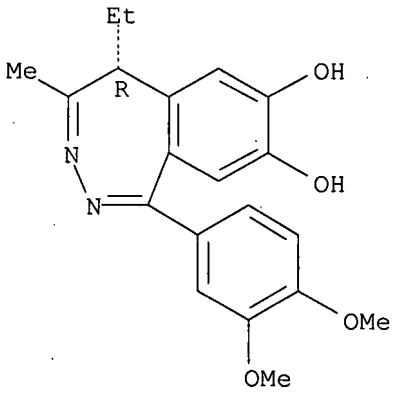


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 7 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 869940-20-5 REGISTRY
ED Entered STN: 15 Dec 2005
CN **5H-2,3-Benzodiazepine-7,8-diol, 1-(3,4-dimethoxyphenyl)-5-ethyl-4-methyl-, (5R)-** (CA INDEX NAME)
FS STEREOSEARCH
MF C20 H22 N2 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



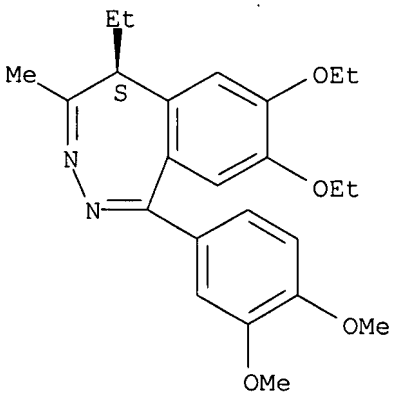
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 8 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 869940-03-4 REGISTRY
ED Entered STN: 15 Dec 2005
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-7,8-diethoxy-5-ethyl-4-methyl-, (5S)-** (CA INDEX NAME)
FS STEREOSEARCH

MF C24 H30 N2 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.

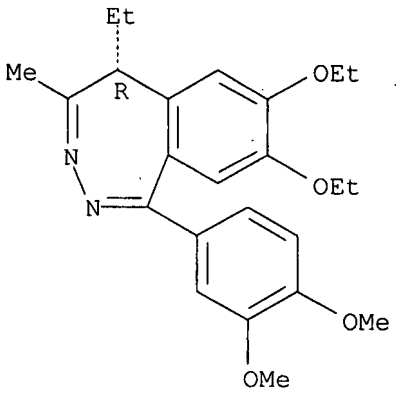


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 9 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 869940-02-3 REGISTRY
ED Entered STN: 15 Dec 2005
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-7,8-diethoxy-5-ethyl-4-methyl-, (5R)-** (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H30 N2 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

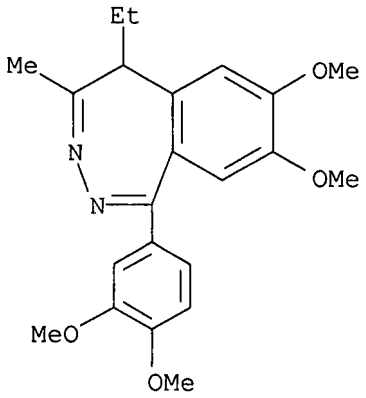
2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 10 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 867020-89-1 REGISTRY

ED Entered STN: 09 Nov 2005
CN **Carbonic acid, dilithium salt, mixt. with 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3-benzodiazepine (9CI)** (CA INDEX NAME)
MF C22 H26 N2 O4 . C H2 O3 . 2 Li
CI MXS
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

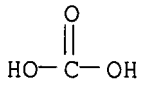
CM 1

CRN 22345-47-7
CMF C22 H26 N2 O4



CM 2

CRN 554-13-2 (463-79-6)
CMF C H2 O3 . 2 Li

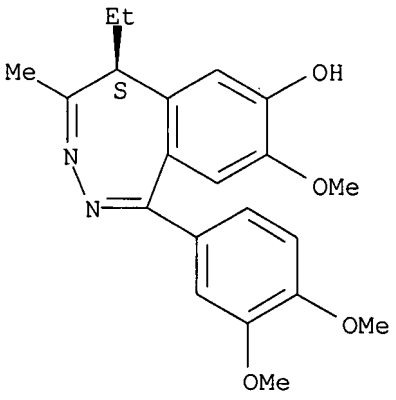


●2 Li

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 11 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 792950-07-3 REGISTRY
ED Entered STN: 06 Dec 2004
CN **5H-2,3-Benzodiazepin-7-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-8-methoxy-4-methyl-, (5S)-** (CA INDEX NAME)
OTHER NAMES:
CN **(S)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine**
FS STEREOSEARCH
MF C21 H24 N2 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.

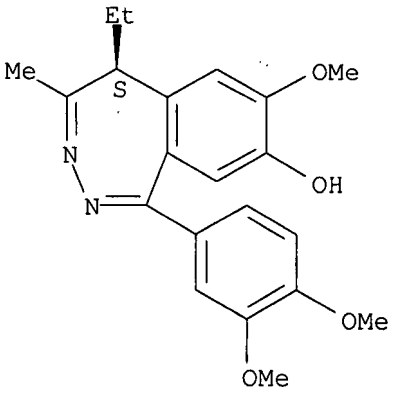


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 12 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 702693-86-5 REGISTRY
ED Entered STN: 02 Jul 2004
CN **5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl-, (5S)-** (CA INDEX NAME)
OTHER NAMES:
CN **(S)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine**
FS STEREOSEARCH
MF C21 H24 N2 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



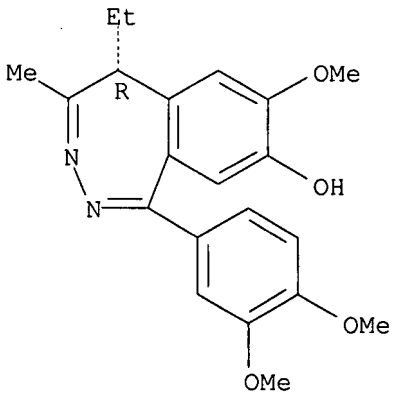
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

6 REFERENCES IN FILE CA (1907 TO DATE)
6 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 13 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 697754-53-3 REGISTRY
ED Entered STN: 23 Jun 2004
CN **5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-**

4-methyl-, (5R)- (CA INDEX NAME)
OTHER NAMES:
CN **(R)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine**
FS STEREOSEARCH
MF C21 H24 N2 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

Absolute stereochemistry.

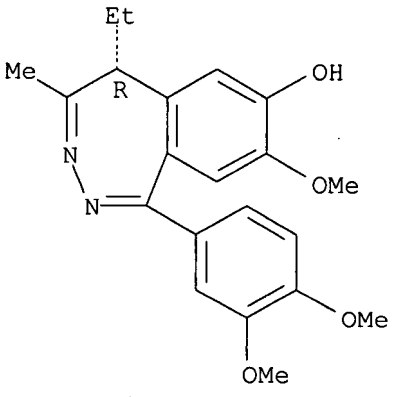


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

9 REFERENCES IN FILE CA (1907 TO DATE)
9 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 14 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 697754-50-0 REGISTRY
ED Entered STN: 23 Jun 2004
CN **5H-2,3-Benzodiazepin-7-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-8-methoxy-4-methyl-, (5R)-** (CA INDEX NAME)
OTHER NAMES:
CN **(R)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine**
FS STEREOSEARCH
MF C21 H24 N2 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

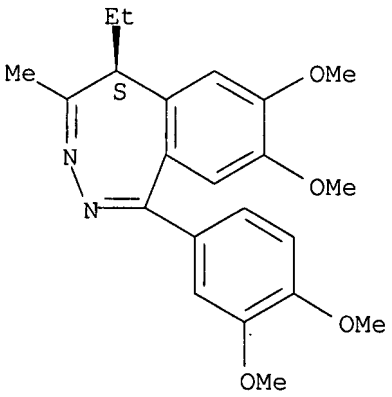
8 REFERENCES IN FILE CA (1907 TO DATE)
8 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 15 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 476625-22-6 REGISTRY
ED Entered STN: 18 Dec 2002
CN **Butanedioic acid, 2,3-bis(benzoyloxy)-, (2S,3S)-, compd. with (5S)-1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3-benzodiazepine (9CI)** (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H26 N2 O4 . x C18 H14 O8
SR CA
LC STN Files: CA, CAPLUS, USPAT2, USPATFULL

CM 1

CRN 82059-51-6
CMF C22 H26 N2 O4

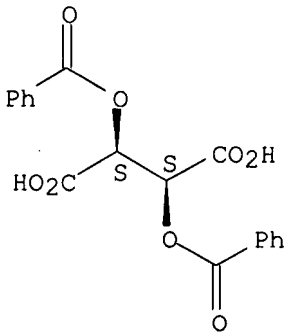
Absolute stereochemistry.



CM 2

CRN 17026-42-5
CMF C18 H14 O8

Absolute stereochemistry. Rotation (+).



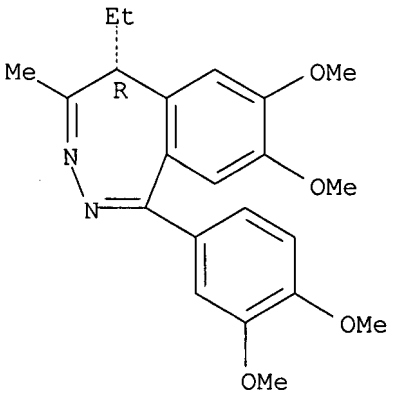
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 16 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 476625-20-4 REGISTRY
ED Entered STN: 18 Dec 2002
CN **Butanedioic acid, 2,3-bis(benzoyloxy)-, (2R,3R)-, compd. with (5R)-1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3-benzodiazepine (9CI)** (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H26 N2 O4 . x C18 H14 O8
SR CA
LC STN Files: CA, CAPLUS, IMSRESEARCH, USPAT2, USPATFULL

CM 1

CRN 82059-50-5
CMF C22 H26 N2 O4

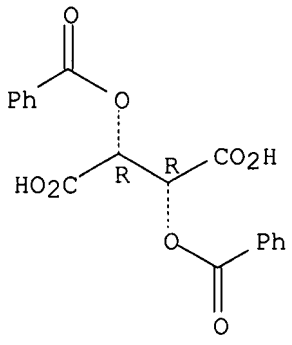
Absolute stereochemistry.



CM 2

CRN 2743-38-6
CMF C18 H14 O8

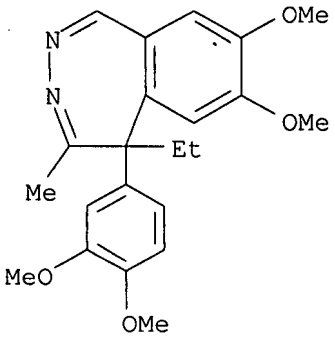
Absolute stereochemistry. Rotation (-).



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

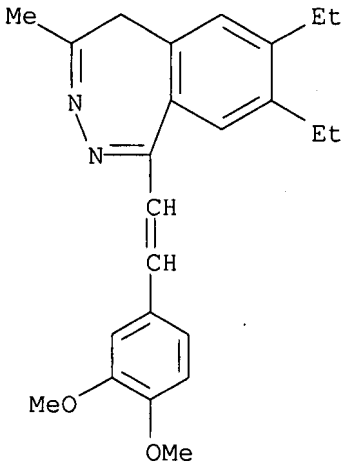
L3 ANSWER 17 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 344259-20-7 REGISTRY
ED Entered STN: 01 Jul 2001
CN **5H-2,3-Benzodiazepine, 5-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-**

4-methyl- (9CI) (CA INDEX NAME)
MF C22 H26 N2 O4
SR Reaction Database



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L3 ANSWER 18 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 181515-97-9 REGISTRY
ED Entered STN: 03 Oct 1996
CN **5H-2,3-Benzodiazepine, 1-[2-(3,4-dimethoxyphenyl)ethenyl]-7,8-diethyl-4-methyl- (9CI)** (CA INDEX NAME)
MF C24 H28 N2 O2
SR CA
LC STN Files: CA, CAPLUS

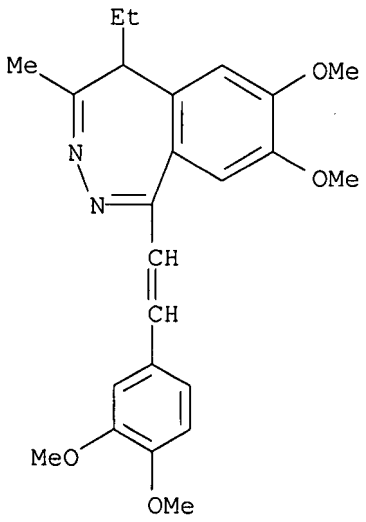


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 19 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 181120-58-1 REGISTRY
ED Entered STN: 24 Sep 1996
CN **5H-2,3-Benzodiazepine, 1-[2-(3,4-dimethoxyphenyl)ethenyl]-5-ethyl-7,8-dimethoxy-4-methyl- (9CI)** (CA INDEX NAME)
MF C24 H28 N2 O4

SR CA
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

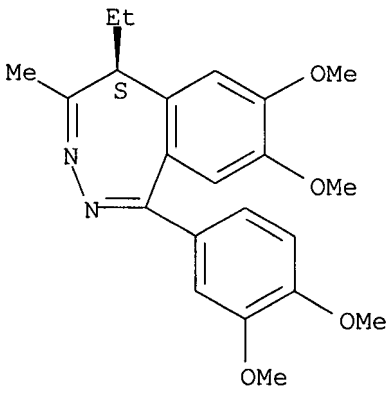
2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 20 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 109575-89-5 REGISTRY
ED Entered STN: 01 Aug 1987
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (S)-, monomethanesulfonate (9CI)** (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H26 N2 O4 . C H4 O3 S
SR CA
LC STN Files: CA, CAPLUS

CM 1

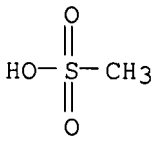
CRN 82059-51-6
CMF C22 H26 N2 O4

Absolute stereochemistry.



CM 2

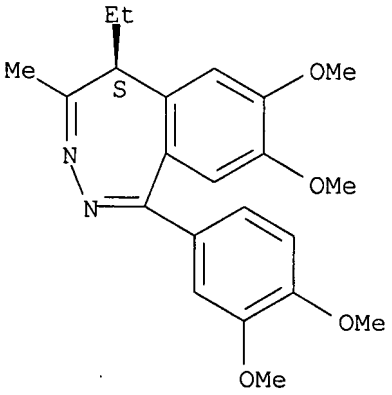
CRN 75-75-2
CMF C H4 O3 S



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 21 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 109575-88-4 REGISTRY
ED Entered STN: 01 Aug 1987
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, monohydrochloride, (S)- (9CI)** (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H26 N2 O4 . Cl H
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS
(*File contains numerically searchable property data)
CRN (82059-51-6)

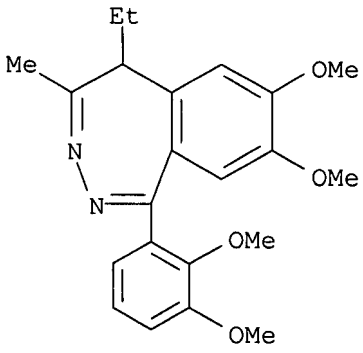
Absolute stereochemistry.



● HCl

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 22 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 104346-54-5 REGISTRY
ED Entered STN: 21 Sep 1986
CN **5H-2,3-Benzodiazepine, 1-(2,3-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (9CI)** (CA INDEX NAME)
MF C22 H26 N2 O4
SR CA
LC STN Files: CA, CAPLUS



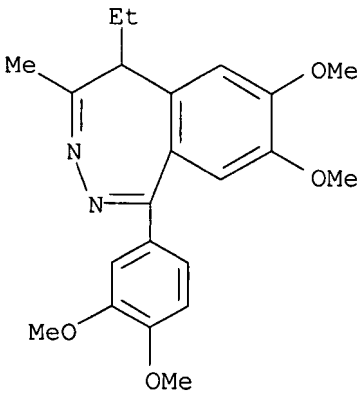
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 23 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 100346-56-3 REGISTRY
ED Entered STN: 22 Feb 1986
CN **Methanol, compd. with 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3-benzodiazepine (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, compd. with methanol (9CI)**
MF C22 H26 N2 O4 . x C H4 O
SR CA
LC STN Files: CA, CAPLUS, IMSRESEARCH

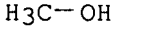
CM 1

CRN 22345-47-7
CMF C22 H26 N2 O4



CM 2

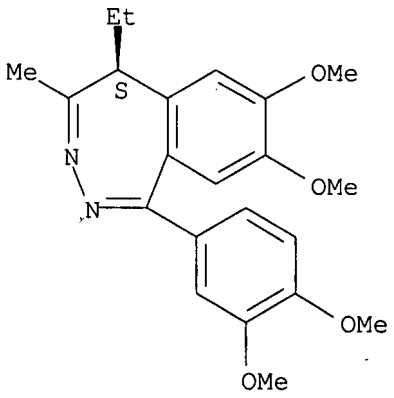
CRN 67-56-1
CMF C H4 O



2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 24 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 98168-49-1 REGISTRY
ED Entered STN: 22 Sep 1985
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, monohydrobromide, (S)- (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN (-)-Tofizopam bromide
FS STEREOSEARCH
MF C22 H26 N2 O4 . Br H
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS
(*File contains numerically searchable property data)
CRN (82059-51-6)

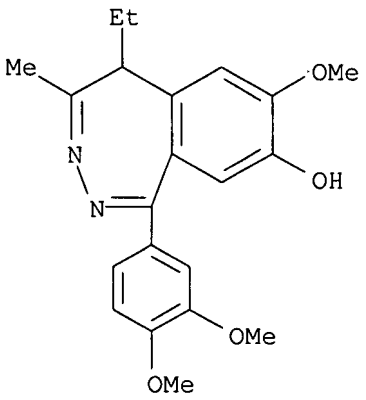
Absolute stereochemistry.



● HBr

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

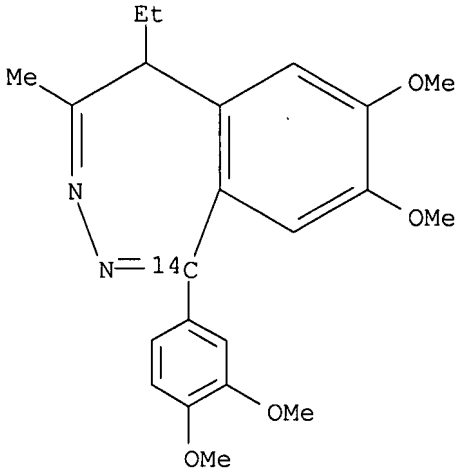
L3 ANSWER 25 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 95500-09-7 REGISTRY
ED Entered STN: 23 Mar 1985
CN **5H-2,3-Benzodiazepin-8-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-7-methoxy-4-methyl-** (CA INDEX NAME)
OTHER NAMES:
CN **1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine**
MF C21 H24 N2 O4
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

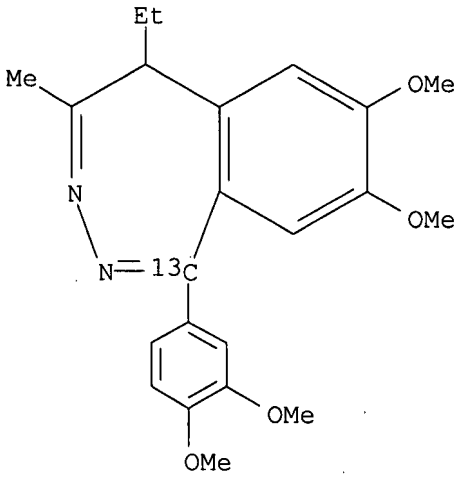
10 REFERENCES IN FILE CA (1907 TO DATE)
10 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 26 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 93635-47-3 REGISTRY
ED Entered STN: 18 Dec 1984
CN **5H-2,3-Benzodiazepine-1-14C, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (9CI)** (CA INDEX NAME)
MF C22 H26 N2 O4
LC STN Files: CA, CAPLUS, CASREACT



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 27 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 90140-61-7 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine-1-13C, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (9CI)** (CA INDEX NAME)
MF C22 H26 N2 O4
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT
(*File contains numerically searchable property data)

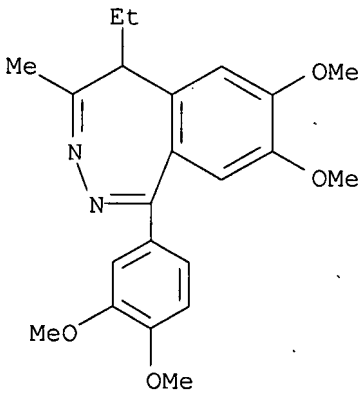


1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 28 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 89664-97-1 REGISTRY
ED Entered STN: 16 Nov 1984
CN **Thiocyanic acid, compd. with 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3-benzodiazepine (1:1) (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, monothiocyanate (9CI)**
MF C22 H26 N2 O4 . C H N S
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, IMSRESEARCH
(*File contains numerically searchable property data)

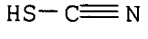
CM 1

CRN 22345-47-7
CMF C22 H26 N2 O4



CM 2

CRN 463-56-9
CMF C H N S



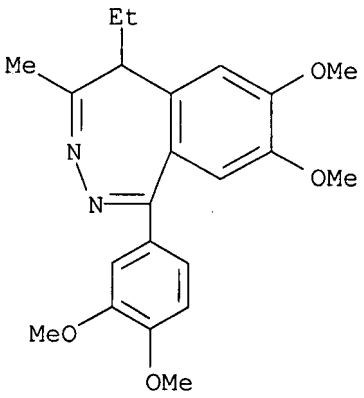
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 29 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 89664-96-0 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, sulfate (1:1) (9CI)** (CA INDEX NAME)
MF C22 H26 N2 O4 . H2 O4 S
LC STN Files: BEILSTEIN*, CA, CAPLUS, IMSRESEARCH
(*File contains numerically searchable property data)

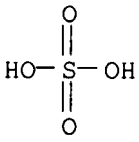
CM 1

CRN 22345-47-7
CMF C22 H26 N2 O4



CM 2

CRN 7664-93-9
CMF H2 O4 S



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

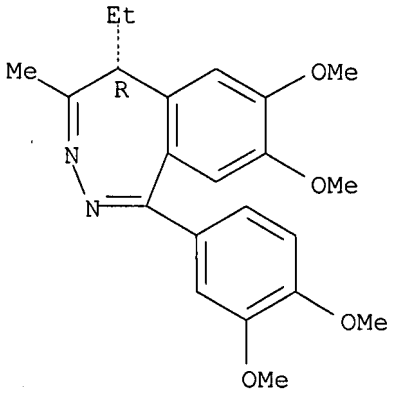
L3 ANSWER 30 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 87584-92-7 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (R)-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:

CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (R)-, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1)**
FS STEREOSEARCH
MF C22 H26 N2 O4 . C4 H6 O6
LC STN Files: CA, CAPLUS, IMSRESEARCH

CM 1

CRN 82059-50-5
CMF C22 H26 N2 O4

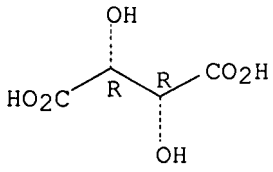
Absolute stereochemistry.



CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.



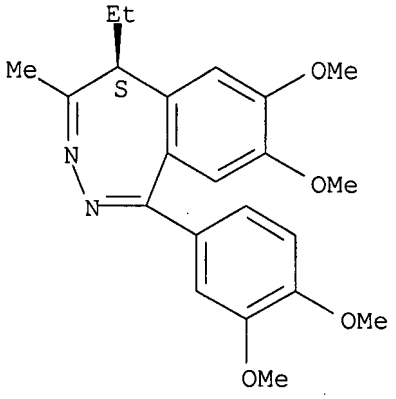
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 31 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 82339-97-7 REGISTRY
ED Entered STN: 16 Nov 1984
CN **Butanedioic acid, 2,3-bis(benzoyloxy)-, [R-(R*,R*)]-, compd. with (S)-1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3-benzodiazepine (1:1) (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (S)-, [R-(R*,R*)]-2,3-bis(benzoyloxy)butanedioate (1:1) (9CI)**
FS STEREOSEARCH
MF C22 H26 N2 O4 . C18 H14 O8
LC STN Files: BEILSTEIN*, CA, CAPLUS
(*File contains numerically searchable property data)

CM 1

CRN 82059-51-6
CMF C22 H26 N2 O4

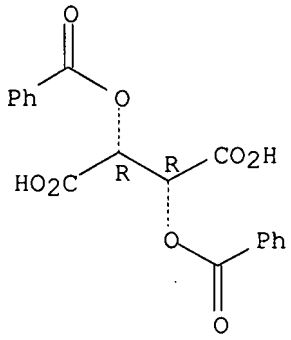
Absolute stereochemistry.



CM 2

CRN 2743-38-6
CMF C18 H14 O8

Absolute stereochemistry. Rotation (-).



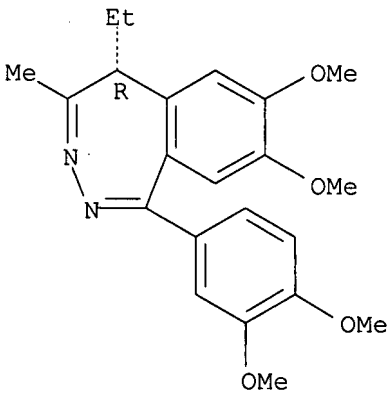
2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 32 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 82339-96-6 REGISTRY
ED Entered STN: 16 Nov 1984
CN **Butanedioic acid, 2,3-bis(benzoyloxy)-, [R-(R*,R*)]-, compd. with (R)-1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3-benzodiazepine (1:1) (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (R)-, [R-(R*,R*)]-2,3-bis(benzoyloxy)butanedioate (1:1) (9CI)**
FS STEREOSEARCH
MF C22 H26 N2 O4 . C18 H14 O8
LC STN Files: BEILSTEIN*, CA, CAPLUS, IMSRESEARCH
(*File contains numerically searchable property data)

CM 1

CRN 82059-50-5
CMF C22 H26 N2 O4

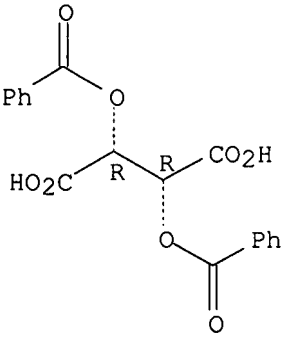
Absolute stereochemistry.



CM 2

CRN 2743-38-6
CMF C18 H14 O8

Absolute stereochemistry. Rotation (-).

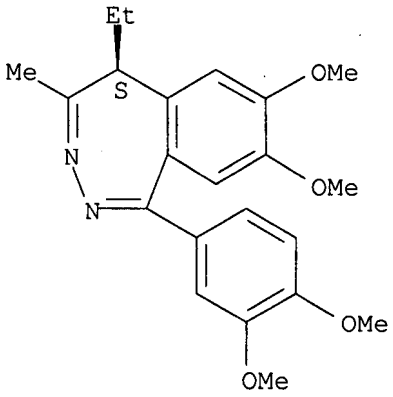


2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 33 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 82059-51-6 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (5S)-** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (S)-**
OTHER NAMES:
CN **(S)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine**
CN (S)-Tofisopam
CN Levotofisopam
FS STEREOSEARCH
MF C22 H26 N2 O4
CI COM
LC STN Files: BEILSTEIN*, CA, CAPLUS, IMSRESEARCH, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL

(*File contains numerically searchable property data)

Absolute stereochemistry.

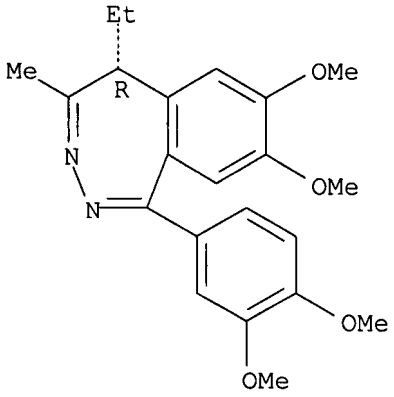


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

31 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
31 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 34 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 82059-50-5 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (5R)-** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (R)-**
OTHER NAMES:
CN **(R)-1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine**
CN (R)-Tofisopam
CN Dextofisopam
FS STEREOSEARCH
MF C22 H26 N2 O4
CI COM
LC STN Files: ADISINSIGHT, BEILSTEIN*, CA, CAPLUS, CBNB, IMSDRUGNEWS, IMSRESEARCH, PHAR, SPECINFO, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)

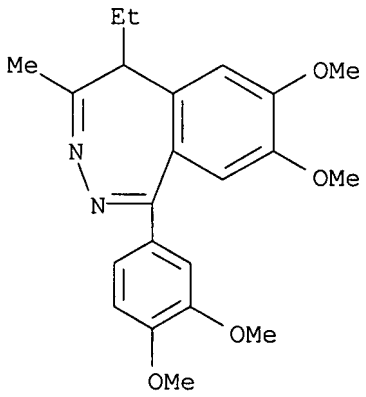
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

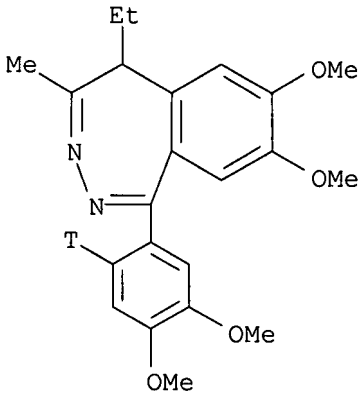
34 REFERENCES IN FILE CA (1907 TO DATE)
34 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 35 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 82005-40-1 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, labeled with deuterium (9CI)** (CA INDEX NAME)
MF C22 H26 N2 O4
LC STN Files: CA, CAPLUS
IL XH-2



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

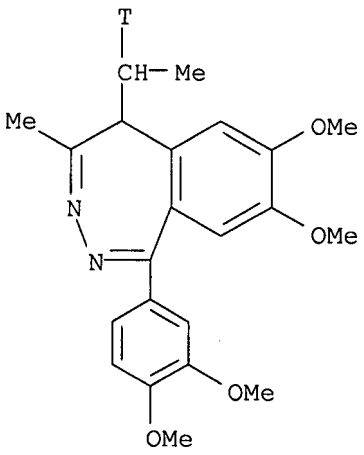
L3 ANSWER 36 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 82005-36-5 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(4,5-dimethoxyphenyl-2-t)-5-ethyl-7,8-dimethoxy-4-methyl- (9CI)** (CA INDEX NAME)
MF C22 H25 N2 O4 T
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

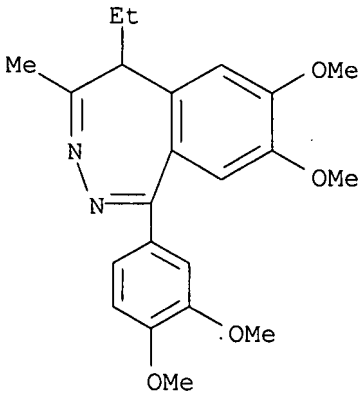
L3 ANSWER 37 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 82005-31-0 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-(ethyl-1-t)-7,8-dimethoxy-4-methyl- (9CI)** (CA INDEX NAME)
MF C22 H25 N2 O4 T
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

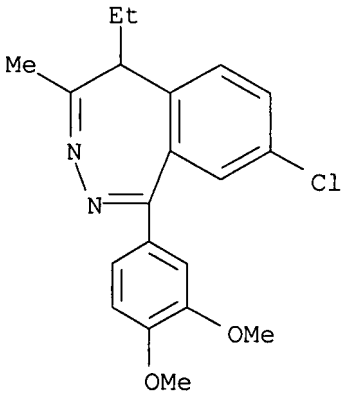
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 38 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 79137-03-4 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, labeled with carbon-14 (9CI)** (CA INDEX NAME)
MF C22 H26 N2 O4
LC STN Files: CA, CAPLUS
IL XC-14



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

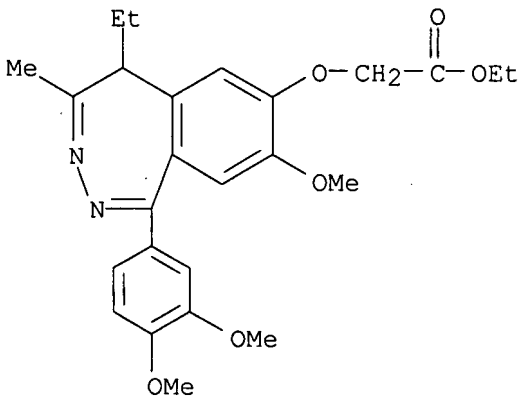
L3 ANSWER 39 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 75113-95-0 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 8-chloro-1-(3,4-dimethoxyphenyl)-5-ethyl-4-methyl- (9CI)** (CA INDEX NAME)
MF C20 H21 Cl N2 O2
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

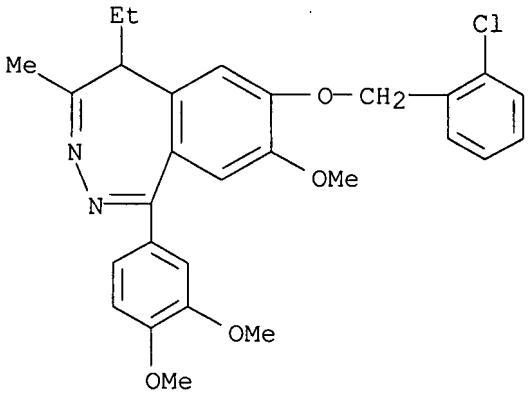
L3 ANSWER 40 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 74950-46-2 REGISTRY
ED Entered STN: 16 Nov 1984
CN **Acetic acid, [[1-(3,4-dimethoxyphenyl)-5-ethyl-8-methoxy-4-methyl-5H-2,3-benzodiazepin-7-yl]oxy]-, ethyl ester (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **5H-2,3-Benzodiazepine, acetic acid deriv.**
MF C25 H30 N2 O6
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

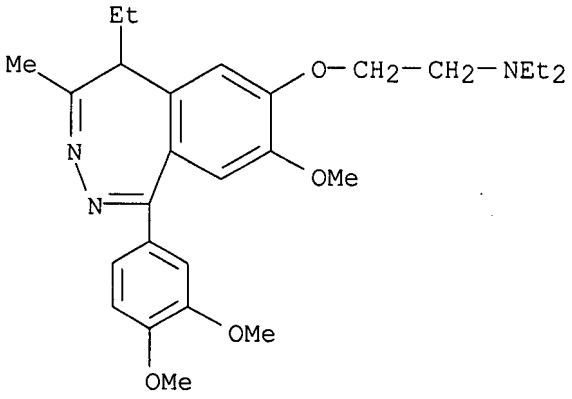
L3 ANSWER 41 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 74950-45-1 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 7-[(2-chlorophenyl)methoxy]-1-(3,4-dimethoxyphenyl)-5-ethyl-8-methoxy-4-methyl- (9CI)** (CA INDEX NAME)
MF C28 H29 Cl N2 O4
LC STN Files: CA, CAPLUS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

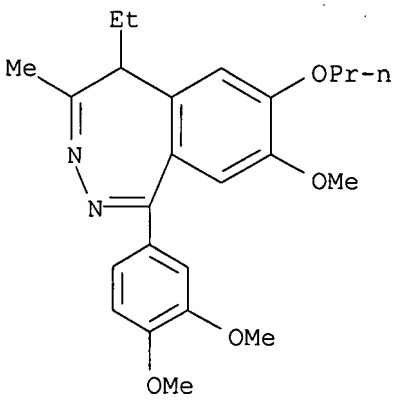
L3 ANSWER 42 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 74950-44-0 REGISTRY
ED Entered STN: 16 Nov 1984
CN **Ethanamine, 2-[[1-(3,4-dimethoxyphenyl)-5-ethyl-8-methoxy-4-methyl-5H-2,3-benzodiazepin-7-yl]oxy]-N,N-diethyl-, dihydrochloride (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **5H-2,3-Benzodiazepine, ethanamine deriv.**
MF C27 H37 N3 O4 . 2 Cl H
LC STN Files: CA, CAPLUS, USPATFULL
CRN (767237-74-1)



●2 HCl

5 REFERENCES IN FILE CA (1907 TO DATE)
5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 43 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 74950-43-9 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-8-methoxy-4-methyl-7-propoxy- (9CI)** (CA INDEX NAME)
MF C24 H30 N2 O4
LC STN Files: CA, CAPLUS, USPATFULL

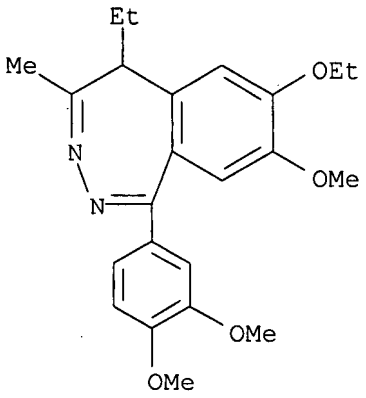


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5 REFERENCES IN FILE CA (1907 TO DATE)
5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 44 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 74950-42-8 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-7-ethoxy-5-ethyl-8-methoxy-4-methyl- (9CI)** (CA INDEX NAME)
MF C23 H28 N2 O4

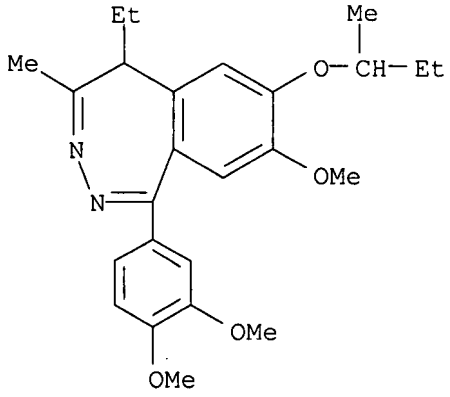
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5 REFERENCES IN FILE CA (1907 TO DATE)
5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 45 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 74950-41-7 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-8-methoxy-4-methyl-7-(1-methylpropoxy)- (9CI)** (CA INDEX NAME)
MF C25 H32 N2 O4
LC STN Files: CA, CAPLUS, USPATFULL

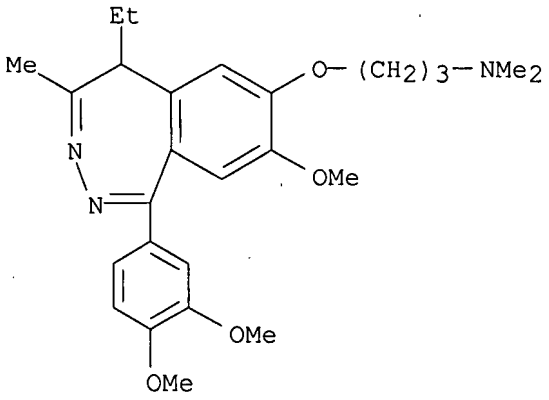


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5 REFERENCES IN FILE CA (1907 TO DATE)
5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 46 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 74950-40-6 REGISTRY
ED Entered STN: 16 Nov 1984
CN **1-Propanamine, 3-[[1-(3,4-dimethoxyphenyl)-5-ethyl-8-methoxy-4-methyl-5H-2,3-benzodiazepin-7-yl]oxy]-N,N-dimethyl- (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **5H-2,3-Benzodiazepine, 1-propanamine deriv.**
MF C26 H35 N3 O4

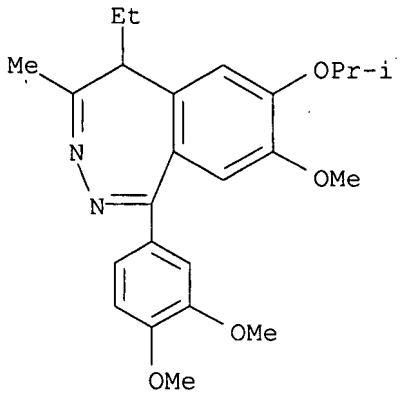
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5 REFERENCES IN FILE CA (1907 TO DATE)
5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

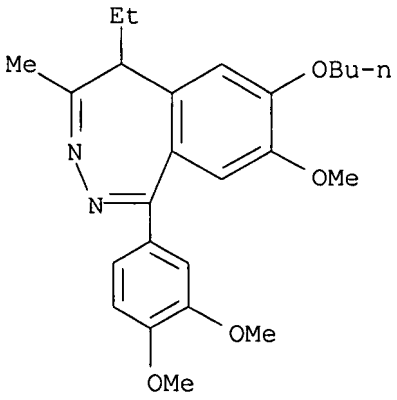
L3 ANSWER 47 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 74950-39-3 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-8-methoxy-4-methyl-7-(1-methylethoxy)- (9CI)** (CA INDEX NAME)
MF C24 H30 N2 O4
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5 REFERENCES IN FILE CA (1907 TO DATE)
5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

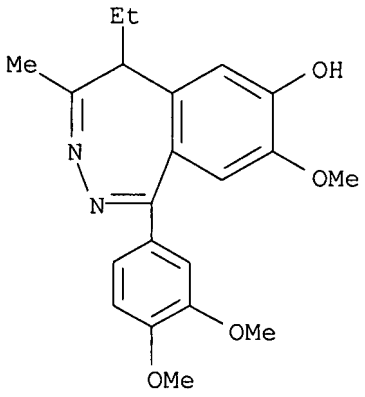
L3 ANSWER 48 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 74950-38-2 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 7-butoxy-1-(3,4-dimethoxyphenyl)-5-ethyl-8-methoxy-4-methyl- (9CI)** (CA INDEX NAME)
MF C25 H32 N2 O4
LC STN Files: CA, CAPLUS, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5 REFERENCES IN FILE CA (1907 TO DATE)
5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 49 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 74950-18-8 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepin-7-ol, 1-(3,4-dimethoxyphenyl)-5-ethyl-8-methoxy-4-methyl-** (CA INDEX NAME)
OTHER NAMES:
CN **1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine**
MF C21 H24 N2 O4
CI COM
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

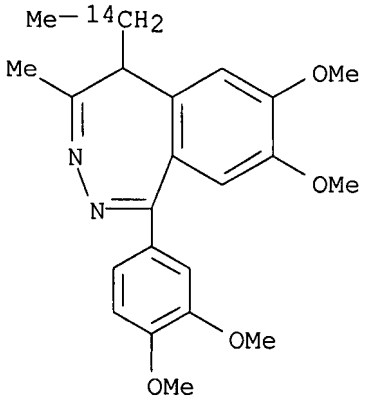


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

15 REFERENCES IN FILE CA (1907 TO DATE)
15 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 50 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 55293-93-1 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-(ethyl-1-14C)-7,8-dimethoxy-4-methyl- (9CI)** (CA INDEX NAME)
MF C22 H26 N2 O4

LC STN Files: BEILSTEIN*, CA, CAPLUS
(*File contains numerically searchable property data)

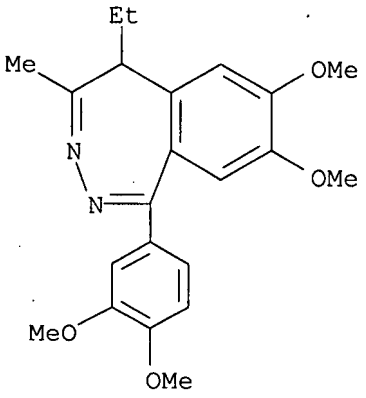


1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 51 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 37952-10-6 REGISTRY
ED Entered STN: 16 Nov 1984
CN **2-Naphthalenol, 4-(3,4-dimethoxyphenyl)-1-ethyl-6,7-dimethoxy-, compd. with 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3-benzodiazepine (1:1) (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, compd. with 4-(3,4-dimethoxyphenyl)-1-ethyl-6,7-dimethoxy-2-naphthalenol (1:1) (9CI)**
MF C22 H26 N2 O4 . C22 H24 O5
LC STN Files: BEILSTEIN*, CA, CAPLUS, IMSRESEARCH, USPATFULL
(*File contains numerically searchable property data)

CM 1

CRN 22345-47-7
CMF C22 H26 N2 O4



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CRN 15462-94-9
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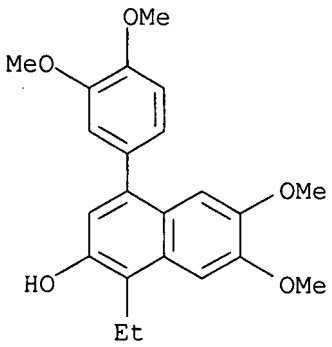
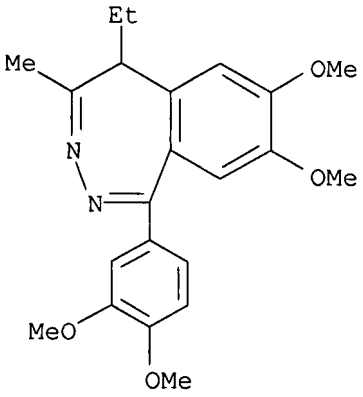


2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 52 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 37952-08-2 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, compd. with 2,4,6-trinitrophenol (1:1) (9CI)** (CA INDEX NAME)
MF C22 H26 N2 O4 . C6 H3 N3 O7
LC STN Files: CA, CAPLUS, IMSRESEARCH, USPATFULL

CM 1

CRN 22345-47-7
CMF C22 H26 N2 O4



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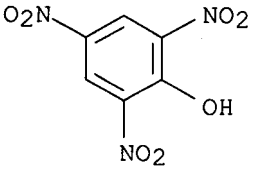

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 53 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 37952-07-1 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, monoperchlorate (9CI)** (CA INDEX NAME)
MF C22 H26 N2 O4 . Cl H O4
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, IMSRESEARCH, USPATFULL
(*File contains numerically searchable property data)

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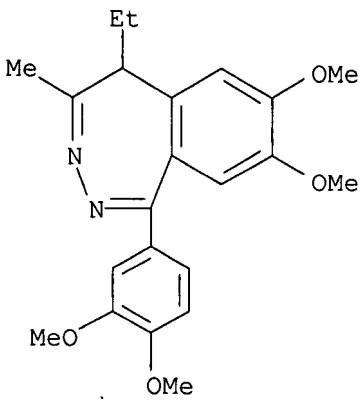
CMF C22 H26 N2 O4



CM 2

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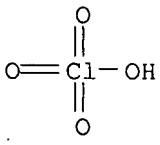
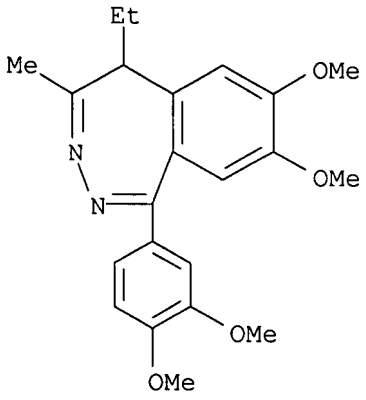
CMF Cl H O4



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 54 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 37952-06-0 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, monohydrobromide (9CI)** (CA INDEX NAME)
MF C22 H26 N2 O4 . Br H
LC STN Files: BEILSTEIN*, CA, CAPLUS, IMSRESEARCH, USPATFULL
(*File contains numerically searchable property data)
CRN (22345-47-7)

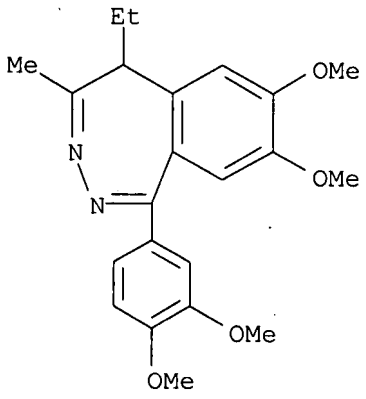


● HBr

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 55 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 37952-05-9 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, monohydrochloride (9CI)** (CA INDEX NAME)
MF C22 H26 N2 O4 . Cl H
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, IMSRESEARCH, USPATFULL
(*File contains numerically searchable property data)
CRN (22345-47-7)



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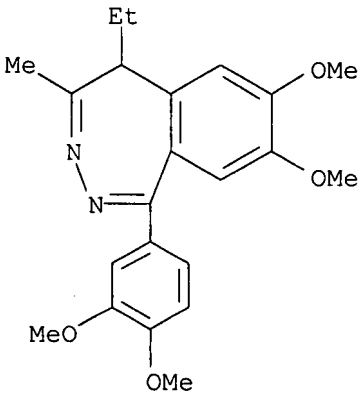
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 56 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 28710-23-8 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, picrate (8CI)** (CA INDEX NAME)
MF C22 H26 N2 O4 . x C6 H3 N3 O7
LC STN Files: CA, CAPLUS, IFICDB, IFIPAT, IFIUDB, IMSRESEARCH, USPATOLD

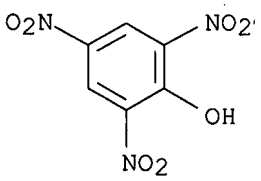
CM 1

CRN 22345-47-7
CMF C22 H26 N2 O4



CM 2

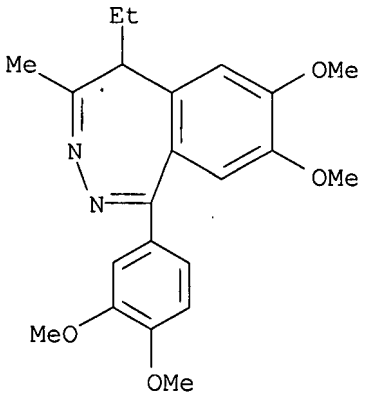
CRN 88-89-1
CMF C6 H3 N3 O7



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 57 OF 57 REGISTRY COPYRIGHT 2007 ACS on STN
RN 22345-47-7 REGISTRY
ED Entered STN: 16 Nov 1984
CN **5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-** (CA INDEX NAME)
OTHER NAMES:
CN **1-(3,4-Dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine**
CN **7,8-Dimethoxy-1-(3,4-dimethoxyphenyl)-5-ethyl-4-methyl-5H-2,3-benzodiazepine**
CN EGYT 341
CN Grandaxin
CN Seriel
CN Tofisopam
DR 87555-18-8
MF C22 H26 N2 O4

CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, PS, RTECS*, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL, USPATOLD
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

211 REFERENCES IN FILE CA (1907 TO DATE)
5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
211 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	162.90	163.11

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FILE LAST UPDATED: 26 Sep 2007 (20070926/ED)

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They are available for your review at:

http://www.cas.org/infopolicy.html

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             5 22345-47-7D
           209 22345-47-7/RN
                 (22345-47-7 (NOTL) 22345-47-7D )
            60 EGYT
          6713 341
             1 EGYT 341
                 (EGYT(W)341)
            36 GRANDAXIN
             0 SERIEL
           157 TOFISOPAM
L5         226 22345-47-7/RN OR EGYT 341 OR GRANDAXIN OR SERIEL OR TOFISOPAM

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         82240 TEMPERATURES
        713930 TEMPERATURE
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       3110798 TEMP
        788649 TEMPS
       3454249 TEMP
                 (TEMP OR TEMPS)
       3619085 TEMPERATURE
                 (TEMPERATURE OR TEMP)
        643624 BODY
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                 (BODY OR BODIES)
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                 (TEMPERATURE OR TEMPERATURES)
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                 (BODY(W)TEMPERATURE)
L6          20 L5 AND (TEMPERATURE OR BODY TEMPERATURE)

=> focus
PROCESSING COMPLETED FOR L6
L7           20 FOCUS L6 1-

=> d ibib abs 1-20 hitstr

L7   ANSWER 1 OF 20  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2004:681397  CAPLUS
DOCUMENT NUMBER:          141:167829
TITLE:                    Method of lowering body temperature
                          with (S)-tofisopam
INVENTOR(S):              Harris, Herbert W.; Kucharik, Robert F.
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 14 pp.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   3
PATENT INFORMATION:
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PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004162284	A1	20040819	US 2003-369823	20030219
WO 2004073638	A2	20040902	WO 2004-US4726	20040217
WO 2004073638	A3	20050113		

W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

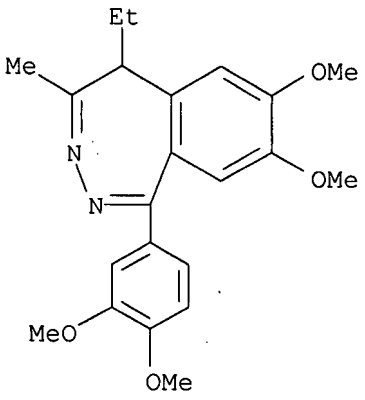
US 2004229866	A1	20041118	US 2004-781422	20040217
US 2004224943	A1	20041111	US 2004-827839	20040419
PRIORITY APPLN. INFO.:			US 2003-369823 A	20030219
			US 2004-781422 A2	20040217

AB (S)-**Tofisopam**, substantially isolated from the corresponding (R)-enantiomer of **tofisopam**, is administered to lower the **body temp.** of an individual.

IT **22345-47-7, Tofisopam**
RL: PEP (Physical, engineering or chemical process); PYP (Physical process); PROC (Process)
(resolution of; (S)-**tofisopam** for lowering **body temp.**)

RN 22345-47-7 CAPLUS

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



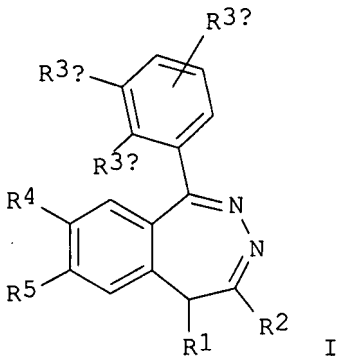
L7 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	2004:964818 CAPLUS
DOCUMENT NUMBER:	141:410972
TITLE:	Preparation of (R)-2,3-benzodiazepine derivatives and method of lowering **body temperature** with them
INVENTOR(S):	Leventer, Steven M.; Kucharik, Robert F.
PATENT ASSIGNEE(S):	USA
SOURCE:	U.S. Pat. Appl. Publ., 22 pp., Cont.-in-part of U.S. Ser. No. 781,422. CODEN: USXXCO
DOCUMENT TYPE:	Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004224943	A1	20041111	US 2004-827839	20040419
US 2004162284	A1	20040819	US 2003-369823	20030219
US 2004229866	A1	20041118	US 2004-781422	20040217
PRIORITY APPLN. INFO.:			US 2003-369823 A2	20030219
			US 2004-781422 A2	20040217

OTHER SOURCE(S): MARPAT 141:410972
GI



I

AB An (R)-2,3-benzodiazepine of formula (I) [R1 = C1-7 hydrocarbyl, C2-6 heteroalkyl; R2 = H, C1-7 hydrocarbyl; or R1 and R2 may combine to form a carbocyclic or heterocyclic 5- or 6-membered ring; R3a, R3b, R3c = H, -O-C1-7 hydrocarbyl, OH, -OC(O)-C1-6 alkyl, -OC(O)O-C1-7 hydrocarbyl, SH, -S-C1-3 alkyl, NH2, -NH-C1-6 alkyl, -N(C1-6 alkyl)2, -NH(:O)-C1-6 alkyl, NO2, halogen; provided at least one of R3a, R3b and R3c is other than H; R4, R5 = -O-C1-7 hydrocarbyl, OH, -OC(O)-C1-6 alkyl, -OC(O)O-C1-7 hydrocarbyl, SH, -S-C1-3 alkyl, NH2, -NH-C1-6 alkyl, -N(C1-6 alkyl)2, -NH(:O)-C1-6 alkyl, NO2, halo; or R4 and R5 may combine to form a 5-, 6- or 7-membered heterocyclic ring], substantially free from the corresponding (S)-enantiomer thereof with respect to the absolute conformation at the 5-position of the benzodiazepine ring, is administered to lower the **body temp**. of an individual. More specifically, the administered compound is (R)-**tofisopam**, or a pharmaceutically-acceptable salt thereof and said individual is afflicted with a disorder associated with an elevated **body temp**. such as fever, malignant hyperthermia, serotonin syndrome, or hot flashes during menopause or perimenopause or occurred as side effects of drug therapy or subsequent to the removal of estrogen-producing tissue. Furthermore said individual is afflicted with a disorder such as cerebral ischemia or stroke wherein therapeutic benefit is achieved by lowering of the **body temp**. to a level below the normal **body temp**. Thus, 4.41 g (10 mmol) 1-(3,4-dimethoxyphenyl)-3-methyl-4-ethyl-6,7-dimethoxyisobenzopyrylium chloride hydrochloride was dissolved in methanol (35 mL) at 40°, cooled to 20-25°, treated with a solution of hydrazine hydrate (0.75 g, 15 mmol)in 5 mL methanol, and allowed to reaction. The reaction was monitored by HPLC and when complete, was evaporated to dryness. The residue is triturated with cold water (3 mL), filtered, and dried to yield crude (RS)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine (racemic **tofisopam**). Racemic **tofisopam** was resolved by chiral chromatog. using a semipreparative Chirobiotic V column (ASTEC, Whippany, New Jersey) and Me tert-Bu ether/MeCN as the eluent to give (R)-**tofisopam** and (S)-

tofisopam. In a stress induced hyperthermia assay using mice, racemic **tofisopam** demonstrated activity in lowering the core **body temp**. (S)-**tofisopam** was more active than either the racemate or the (R)-enantiomer. However, the (R)-enantiomer showed greater tolerability compared with either the racemate or the (S)-enantiomer. For example, the mice treated with the (R)-enantiomer showed less sedation, abnormal gait, or ptosis, decreased muscle tone, decreased lacrimation, or decreased reactivity to touch compared with either (S)-enantiomer or the racemate.

L7 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:577894 CAPLUS
DOCUMENT NUMBER: 145:62931
TITLE: Method of isolating (R)-**tofisopam**
INVENTOR(S): Perrin, Scott R.; Ye, Naidong; Galbraith, Kimm B.; Hauck, Wilhelm
PATENT ASSIGNEE(S): Vela Pharmaceuticals, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 24 pp., Cont.-in-part of U.S. Ser. No. 841,075.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006128955	A1	20060615	US 2005-305490	20051215
US 2004254174	A1	20041216	US 2004-841075	20040507
US 7265106	B2	20070904		
WO 2007078808	A2	20070712	WO 2006-US47656	20061213

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RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

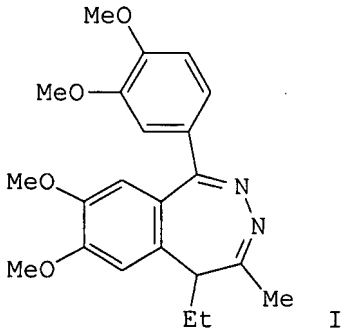
PRIORITY APPLN. INFO.:

US 2003-469456P	P	20030509
US 2004-841075	A2	20040507
US 2005-305490	A	20051215

AB The present invention is directed to a process for the isolation of (R)-**tofisopam** with high enantiomeric purity and high overall yields from a mixture of **tofisopam** enantiomers by means of a non-steady state continuous chromatog. process. Isolation of (R)-**tofisopam** from a mixture of **tofisopam** enantiomers, i.e. (R)-(-), R(+)-, (S)-(-)-, and (S)-(+)-**tofisopam**, was carried out in a nonsteady state continuous separation process (VariCol process) using 5 2.5 cm (i.d.)+10.6 cm chromatog. columns packed with CHIRALPAK 61161, a chiral separation medium comprising amylose tris(3-chloro-4-methylbenzoate) coated on silica, which were connected in series in a loop. Multiple inlets and outlets were placed in the loop between the columns. After the system was stabilized by passing MeCN through the columns, a solution of **tofisopam** enantiomers in MeCN (concentration 48-50 g/L) was continuously injected into the system. The separation was performed using the various **temps**., feed concns. and flow rates to give 78.3% (highest yield) (R)-**tofisopam** (highest purity 99.5%).

L7 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN

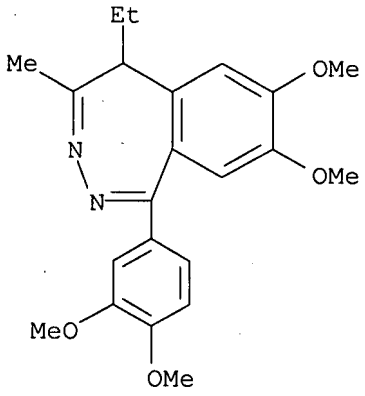
ACCESSION NUMBER: 1979:34556 CAPLUS
DOCUMENT NUMBER: 90:34556
TITLE: Analytical investigation of **tofisopam**
AUTHOR(S): Benko, Andras
CORPORATE SOURCE: Orsz. Igazsagugyi Vegyeszeti Intez., Budapest, Hung.
SOURCE: Acta Pharmaceutica Hungarica (1978), 48(6), 241-5
CODEN: APHGAO; ISSN: 0001-6659
DOCUMENT TYPE: Journal
LANGUAGE: Hungarian
GI



I

AB Methods are given for the detection and determination of **Grandaxin** (**tofisopam**)(I) [**22345-47-7**] in forensic medicine. Seven solvents, described in the literature, were compared for the thin-layer chromatog. separation of I from diazepam and nitrazepam. Gas chromatog. was carried out on OV-101 on Gaschrom Q, using a flame-ionization detector and N carrier gas. The column **temp**. was 310°. The determination threshold was 1 μg. For UV spectrophotometry, the anal. line was 311 mm.

IT **22345-47-7**
RL: ANT (Analyte); ANST (Analytical study)
(determination of, in legal chemical)
RN 22345-47-7 CAPLUS
CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)



L7 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1983:499217 CAPLUS
DOCUMENT NUMBER: 99:99217
TITLE: **Tofisopam**, a new 2,3-benzodiazepine.

Inhibition of changes induced by stress loading and hypothalamic stimulation

AUTHOR(S): Yamaguchi, K.; Suzuki, K.; Niho, T.; Shimora, M.; Ito, C.; Ohnishi, H.

CORPORATE SOURCE: Fuji Cent. Res. Lab., Mochida Pharm. Co., Ltd., Gotemba, 412, Japan

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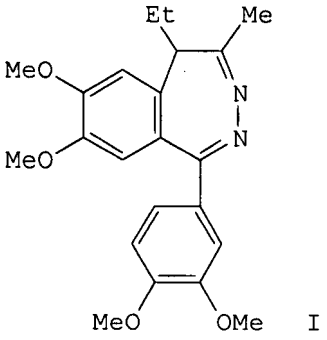

I

AB Effects of **tofisopam** (I) [**22345-47-7**] on gastric ulceration induced by water-immersion stress in normal rats and by immobilization stress in olfactory-bulbectomized (OB) rats were investigated along with propulsion of the small intestine caused by water-immersion stress in rats and autonomic responses to elec. stimulation of the hypothalamus in rabbits. In the latter, the results were compared with those of diazepam and γ-oryzanol. **Tofisopam** (30 and 100 mg/kg, orally) inhibited the gastric ulceration induced by water-immersion stress in normal rats in a dose-dependent manner. Immobilization-stress loading increased the incidence and average index of gastric ulceration in OB rats, compared with nonstressed rats. **Tofisopam** inhibited the gastric ulceration induced by stress loading in OB rats. Water-immersion stress loading induced an increase in intestinal propulsion in rats. This increase was reversed to control levels by **tofisopam**. **Tofisopam** (1.0 mg/kg, i.v., or 0.1 mg/kg by intracerebrospinal injection) inhibited the constriction of ear microvessels, the decrease in earlobe **temp**., and mydriasis induced by elec. stimulation of the medial hypothalamic area in rabbits. However, diazepam and γ-oryzanol failed to inhibit the autonomic responses to medial hypothalamic stimulation. Thus, **tofisopam** restores the autonomic abnormality induced by stress loading possibly via intervention in the central autonomic area, i.e., the hypothalamus, by an action different from that of diazepam.

IT **22345-47-7**
RL: BIOL (Biological study)
(hypothalamus stimulation- and stress-induced changes response to)

RN 22345-47-7 CAPLUS

CN 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl- (CA INDEX NAME)

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Use of health services by the climacteric women in primary health care: The need for an integral approach

Amelia Rodríguez Martín[1], Mª MAR Fernández del Barrio[2], Teresa Fernández del Bar
Pedro Arango Fernández[3] & Juan Martín Tello[3]
[1] University of Cádiz, Spain; [2] The Salus Infirmorum Nursing School, Spain; [3] Rodríguez Arias Health Center, San Fer (Cádiz), Spain

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Abstract. During the climacteric, women experience multiple health problems. As their needs are not catered for in an integral fashion due to the lack of any specific programme or mechanism to provide for this, they show an increased use of the health services, and an increased rate of referrals to different specialists. This study, carried out in a Basic Health Zone in San Fernando (Cádiz, Andalusía, Spain) on a sample of climacteric women who attended the Health Centre during 1995, examines these points and shows a significantly higher use of the health services in relation to the rest of the female population (those who are not in the climacteric age group) as well as a high percentage of referrals (74.6%) to specialists. It was found that both the level of knowledge about the climacteric and the use of the health services influenced by the educational level ($p < 0.001$ age ($p < 0.05$). Women who felt that their fa provided an understanding and supportive at were found to have less psychological problems consequently, less consultations and referrals fo reason ($p < 0.00001$). The authors hope that findings will provide a basis for the setting up programme of integral health care for clima women at the level of primary health care. careful planning and the drawing up of a str plan, it would be possible to provide for the ne this population group in a more satisfactory wa it would also permit a rationalization of the resc available.

Key words: Climacteric, Health promotion, Level of knowledge, Use of health services

Introduction

Both the directives issued by the Spanish Ministry of Health and Consumption and the Health Plan for Andalusía contemplate the possibility of providing integral and protocolised care for climacteric women at the level of primary health care (Health Plan for Andalusía, 1993).

In reality, however, each symptom is dealt with separately under different subprograms. It is only at the tertiary level in the Spanish Health Services that we find specific menopause units and, due to the high level of specialisation and the difficulty of access, these usually have a low level of catchment (1.5% in Cádiz, Andalusía, Spain in 1995).

worthy of attention given that more than a thi the total female population will belong to thi group and that it constitutes a considerable peri a woman's life during which she is suffering fro corresponding symptoms and health problems.

During this time women usually experier number of symptoms and disorders attributal the decline in the endocrine function of the ov Authors such as Bedoya, Fritz, Jones, and M [4–7] speak of 'short term' symptoms (hot fl menstrual irregularities, insomnia, anxiety, d sion), 'medium term' symptoms, especially ge sexual (decline of libido, painful sexual interc and urinary tract problems (urinary incontinenc urinary infection among others) and 'long

at the level of Primary Health Care, to provide them with easier access to solutions for their health problems.

The study, which is descriptive, was based on a small area, the Basic Health Zone (BHZ) Rodríguez Arias in San Fernando (Cádiz, Andalusía, Spain) which is fully identifiable from a geographic, demographic and epidemiological point of view, covering a population of 25,000 inhabitants (32% of the population of San Fernando). The demographic characteristics of this Basic Health Zone are representative of other Basic Health Zones, not only in the province of Cádiz, but also Andalusía.

The Health Centre is staffed by general practitioners, pediatricians, nurses, one social worker, one veterinary surgeon and auxiliary staff. The specialist consultants, including gynaecologists are in the main public hospital 'Puerta del Mar', which is 10 km away from the Health Centre, and has a Menopause Unit.

The aims of the study were:

1. To ascertain the average age of the climacteric women in the BHZ studied.
2. To ascertain the degree of use of health services by the women in the BHZ, aged from 40–57 years (climacteric), and the non-climacteric female population (12–39 years and 58 years plus) during 1995.
3. To consider some of the variables which may lead to a greater or lesser use of the health services, such as age and educational level.
4. To determine the principal motives which lead these women to consult their doctor.
5. To determine the degree of referrals of the climacteric women studied to other levels of the health service.
6. To determine the level of knowledge about the climacteric of the climacteric women in the BHZ and the possible relation with their use of the health services, their educational level and their age.
7. To determine how much family support these women receive and to evaluate what influence this factor may have on the appearance of psychological disorders and related medical consultations.

Materials and methods

A descriptive, correlational study was carried out for

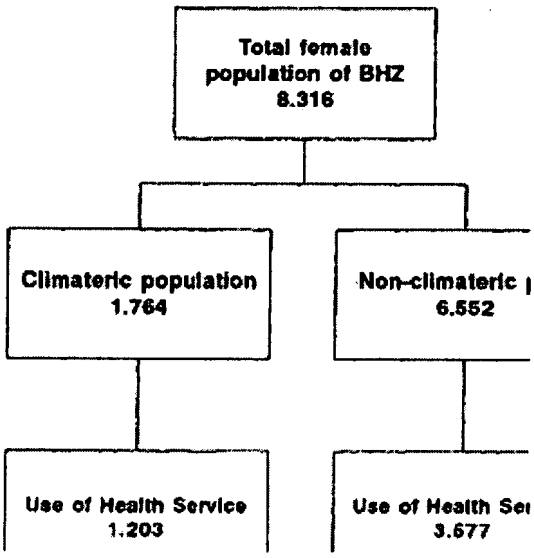
1.764% climacteric women and 6.552% non acteric women (12–39 years or 58 years plus though the group of non-climateric women cc wide age range, adolescents and women ov years represent a low percentage of the popu corresponding to the Rodríguez Arias Health C and their consultations were minimal (the f because of their generally good state of healt the latter because they have a higher percenta home visits). For this reason possible distorti the results due to the wide age range is minima vast majority of the women who consulted doctor at the Health Centre were between 30 a years of age.

From the appointment records of the Rod Arias Health Centre for 1995, information wa tained corresponding to the women in each who had used the health services, that is, the consulted their family doctor in the Health C This was the reference population for the study which the sample was taken.

The calculation of the size of the sampl computer aided (Epi-Info 5.0) using this gro women for an expected frequency of 50% a confidence interval of 95%. There were found 291 climacteric women and 347 non-clima women.

Subsequently, sample women were select random from the appointment records for each groups to be studied (Figure 1).

A form was drawn up to include: person formation (age and educational level, among



ers), reasons for consultation, referrals and reasons for the same, excluding the usual screening for the age group. This data was obtained from the monitoring sheets in the clinical histories of the women to be studied.

The information referring to the non-climacteric sample of the population, which was taken from the appointment records of the Health Centre for 1995, was limited by the number of consultations made for that year.

A questionnaire was also drawn up comprising a series of questions to ascertain the level of knowledge of the women in the sample about the climacteric, including: the age at which the climacteric usually begins, accompanying symptoms and their identification, the existence of treatment and if they had requested it.

In anticipation of the possible answers to these questions, three levels were established to reflect the level of knowledge:

- low: 0–3 correct answers.
- medium: 4–7 correct answers.
- high: 8–11 correct answers.

The questionnaire also covered information about the climacteric that the women had received from their doctors, and if they felt that their family were supportive and understanding.

Once the questionnaire had been drawn up it was validated and no corrections were found to be necessary. The questionnaire was applied to the 291 selected climacteric women during home visits by 4 doctors and one nurse, having previously agreed on the criteria and procedure to be followed.

The information obtained was processed with the aid of a computer (Epi-Info 5.0).

For the comparison of the proportions, the χ^2 test with the correction of Yates was used to obtain a confidence interval of 99%. Anova and Bartlett's test of homogeneity and variance were also applied for the comparison of averages when they were considered necessary.

Results

The total population of climacteric women belonging to the Health Centre who consulted their doctor in 1995 on at least one occasion was 1203 (68%), generating 13,582 visits, whereas the number of women of the non-climacteric population over 12

The average age of the climacteric women wa years with a standard deviation of 1.5 years.

Regarding the educational level of the wc 27.9% (79 women) had no schooling, 40.7% women) had primary education, 21.9% (62 wc had secondary education and 9.6% (27 women received further and/or university education.

An Anova test, to compare the average use health services with the educational level o women showed that those with a higher educa level used the health services less versus no-scho primary-education and secondary-education w ($p < 0.01$).

Bartlett's homogeneity of the variance showe the average use of the health services varied si cantly according to the age of the woman, anc younger women used the health services ($p < 0.01$).

The principal motives for consultation wit family doctor are shown in Table 1, where we ca that rheumatic symptoms (pains in the joints) the prime reason for 591 visits (18.5%), follow cardiovascular pathology (principally high pressure and alterations in the heart beat) wit visits (14%), genital or sexual complaints (al detailed in the introduction) caused 362 (11.3%), psychological symptoms (anxiety, de sion) 359 visits (11.3%), hot flushes 346 (10.8%), disorders of the metabolism 342 (10.7%), urinary infections 283 visits (8.9%) other motives which do not come into the pre categories with a total of 188 visits (5.9%). In 8.3 the total number of visits the motive for the cc tation does not figure in the patient's clinical re

74.6% of the climacteric women were referre specialist at some time, with an average of 1.7 ferrals per woman and year. Routine screening i age group, such as cervical smears or mamm phies were not included.

Of the total number of referrals, the highest centage were due to rheumatic causes which ca 28,125, followed by genital complaints 23%, m olism disorders 14.3%, cardiovascular prol 14.1%, psychological complaints 12.5%, urina fections 7.1% and other reasons 1%.

Table 1. Reasons for consultation with a family doct the climacteric women (n = 291)

Symptoms	N	%

These percentages can be misleading, because when we calculate the rate of referrals according to symptoms (the frequency of referral for each reason for every 100 consultations for the same reason) as is shown in Table 2, we find that the consultations made for genital and/or sexual problems lead to the highest number of referrals, 32%, followed by rheumatic symptoms 24%, metabolism disorders 21.1% and psychological problems 17.6%.

Overall, as was previously mentioned, three levels were established to reflect the women's level of knowledge about the climacteric, according to their answers to the questions shown in Figure 2. 42.8% of the women were found to have a high level of knowledge, 40.6% a medium level and 16.6% a low level.

One of the questions which figured in the questionnaire to ascertain the level of knowledge was to determine if the climacteric women knew of the existence of hormone replacement therapy (HRT). 61% claimed to know of it but only 30% of the women questioned had requested the treatment.

No statistically significant difference was found to relate the level of the women's knowledge about the climacteric and the degree of use of the health services.

On the other hand there was an appreciably significant statistical difference in the age and educational level of the women related to their knowledge about the climacteric: the higher the educational level and the younger the woman ($p < 0.05$), the higher the level of knowledge was about the climacteric ($p < 0.001$).

Finally, it was observed that 65.7% of the women felt that their families were supportive and when they were supported they showed less psychological problems and, consequently, the less they consulted their doctor for this reason ($p < 0.00001$).

Discussion

The average age of the women in the climacteric phase obtained at the Basic Health Zone studied is similar to that described by the majority of authors, who find that it occurs at fifty years of age, with a

Table 2. Referrals

Cause	%	Rate[a]

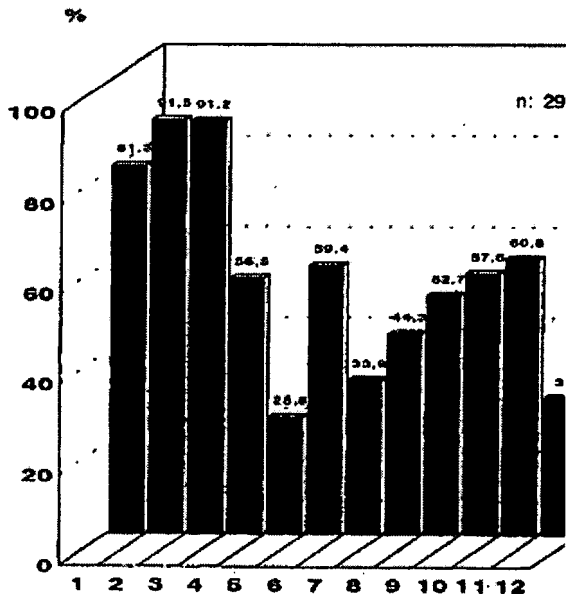


Figure 2. Symptoms and knowledge about the clim syndrome among climacteric women in the popu sample.

standard deviation of 1.5 years [1]. This is sl higher than that found by Mayer and Linsco Hughes [9], Comino [2] and the Spanish Soci Gynaecology and Obstetrics, which varies fron to 47 years in the last case [4].

Although the great use of the health services part of this group of women has been pointed authors such as Barlow and Borrell [10, 11] th not been correlated with the use of services remaining groups of women.

The principal motives for which the clim women in our Basic Health Zone consulted th tor were comparable with the findings of Barlo and Jiménez de Luque [12] among others, the frequent reasons were symptoms associated rheumatic, cardiovascular, genital and sexual lems. It has not been our concern in this study, been the case with some other authors [13] to co

educational level have a significant influence on the magnitude of the problem; following this line, we have found no studies which consider the possible relation between these variables and the use of the health services.

There was a strikingly high percentage of women who had no schooling (285) and of women with only primary education (41%). This is in fact typical for middle-aged women in most rural areas in Spain, due to the economic depression after the Spanish civil war heat did not encourage women's education. The situation is very different today thanks to compulsory education and a change of mentality in relation to women.

The results obtained for the symptoms identified with the climacteric period by the women in our sample were observed to be similar to those of Mayer and Linscott [8], Randall [14] and Barlow [10] who found hot flushes and aching joints as the most frequently symptoms identified by the climacteric women.

Tropeano et al. [15] and Tejerizo [16] give particular importance to the fact that the women who felt that their families gave them support and understanding appeared to have less problems of a psychological nature and ask for less help for these motives. This is in consistence with the results obtained in our study.

Conclusions

1. The use of the health services by the climacteric women of the Rodriguez Arias Basic Health Zone in San Fernando (Cádiz) during 1995 was significantly superior to that of non-climacteric women for the same period of time.
2. The principal motives for consultation were rheumatic, followed by cardiovascular and genital and/or sexual problems.
3. There is a statistically significant relation between the use of the health services by climacteric women and their educational level and age.
4. There is a high degree of referral to second or third degree health care for the climacteric women who used the health services.
5. The climacteric women in the Rodriguez Arias Health Zone in San Fernando (Cádiz) have a medium–high level of knowledge about the climacteric process. Younger women, with a higher educational level, have more knowledge about the

level of Primary Health Care. This is a possi
which is included in the Spanish legisl
through the Goverment Health Programm
the Autonomy of Andalusia, but which has
yet been put into practice. However, in vi
daily experience, the results of this study an
recommendations of a number of different au
[17–20], the present authors feel that a pl
action should be designed with three main a
To create a mechanism which provides for the
care of the climacteric woman in the Basic H
Zone (BHZ) within the Health Centre: A Pri
Health Care Menopause Unit (PHCMU). Thi
would be made up of a multidisciplinary team
sisting of a family doctor, nurses, a social worke
psychologist.

To give counselling in the family environment
climacteric woman of the BHZ under the care
Unit, in those cases where it is considered to be
udicial to the psychological welfare of the wom

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Address for correspondence: Dra. Amelia Rodríguez ín, Escuela de Ciencias de la Salud, Area de Salud I Avda. Duque de Nájera, 18, 11002 Cadiz, Spain
Phone: 212988; Fax: 214218
E-mail: amelia.rodriguez@uca.es